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A CASE OF RECURRENT THROMBOSIS ASSOCIATED WITH THE LOW RESPONSE OF PLASMINOGEN ACTIVATOR AND THE HIGH RESPONSE OF FACTOR VIII: C FROM THE VESSEL WALL BY DDAVP INJECTION

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ABSTRACT

A case of cerebral thrombosis is described in which the low level of plasminogen-activator release and the high level of factor VIII: C release from the vessel wall by 1-deamino-8-D-arginine vasopressin (DDAVP) injection was thought to have some relation to the occurrence of the patient's thrombotic tendency. We could not confirm whether this abnormality in the response to DDAVP injection is hereditary or not. But the DDAVP injection test was considered to be a useful technique for detecting abnormality in the vessel wall.

INTRODUCTION

Recently, cerebrovascular diseases and malignant cancers have become the two main causes of death in Japan, and in cerebrovascular diseases, cerebral thrombosis occurs more often than cerebral haemorrhage. Thrombotic diseases including cerebral thrombosis, pulmonary embolism, deep vein thrombosis and myocardial infarction are sometimes caused by some underlying diseases, such as diabetes mellitus or arteriosclerosis (1,

2).

An abnormality in the blood coagulation system itself, i. e, antithrombin III deficiency or abnormality, plasminogen abnormality, could also cause thrombotic diseases (3, 4). In addition to these abnormalities, an abnormality in the coagulation-fibrinolysis balance in the vessel wall could also be the cause of these thrombotic tendencies.

It is reported that the injection of a small dose (0.3-0.4 μg/kg) of DDAVP can produce the release of factor VIII and plasminogen activator from the vessel wall, and that this is a reliable method to evaluate the coagulation-fibrinolysis balance in the vessel wall (5, 6). We found that even a smaller dose (0.1-0.2 μg/kg) of DDAVP could produce this release reaction.

In this paper, we report on a case of recurrent thrombosis. The patient was young and was free from any of the underlying diseases mentioned above. He showed a low level of plasminogen activator release and high level of factor VIII release after the injection of a small dose of DDAVP.

Materials and Methods

Coagulation-fibrinolytic assay methods (7): Prothrombin time (PT), activated partial thromboplastin time (aPTT) and euglobulin lysis time (ELT) were assayed by the usual method, factor Xa and thrombin were assayed using chromogenic substrate (S-2222 and S-2238), factor VIII coagulant activity assays were performed by using coagulation factor deficient plasma (one stage method) (normal range: 60-120 %). Factor VIIIR: Ag (normal range: 136.0±73.1 %), plasminogen (normal range: 8.6-13.2 mg/dl) and plasminogen activator (plg-act) (normal range: 0.16 urokinase units/ml, using S-2251, Kabi Co.) were also determined.

Materials: 4 or 8 μg of DDAVP was injected intravenously to a normal young group (21-31 years old, 5 males and 5 females) and an elder group (52-60 years old, 2 males and 2 females). Blood was collected using 3.8 % sodium citrate as an anticoagulant at the ratio of 9 to 1, and centrifuged at 3,000 rpm at 4 °C for 15 min to obtain the test plasma. Platelet aggregation test was performed using ADP (10^{-5} or 10^{-6}M), epinephrine (10^{-5} M) and collagen (5 μg/ml). Blood samples were collected from patients who were admitted to the Kuwana Hospital and their families.

Results

(1) Injection of 4 or 8 μg of DDAVP to normal controls:

APTT shortened after 5 to 300 min of DDAVP injection in both doses, and the shortening in aPTT was more remarkable in the younger group than in the elder group. PT did not change significantly. Factor VIII: C and factor VIIIR: Ag increased significantly at the time of 5 to 300 min in both doses of DDAVP. The values of both were higher in the elder group than in the younger group before and after the injection of DDAVP (Fig. 1 and 2). Plasminogen activator increased slightly at the time of 5 to 60

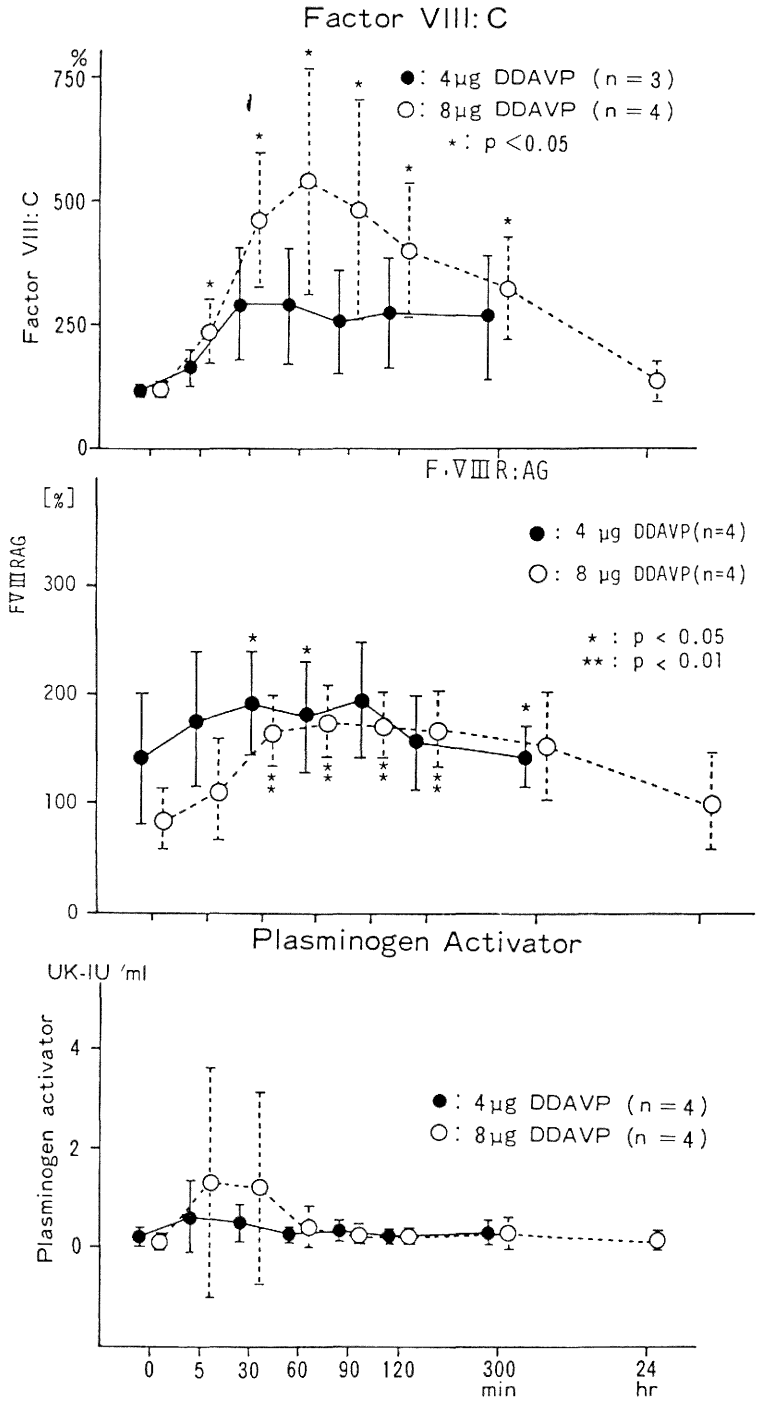

Fig. 1 Changes of factor VIII: C, VIIIR: Ag and plasminogen activator after injection of 4 or 8 μg of DDAVP.

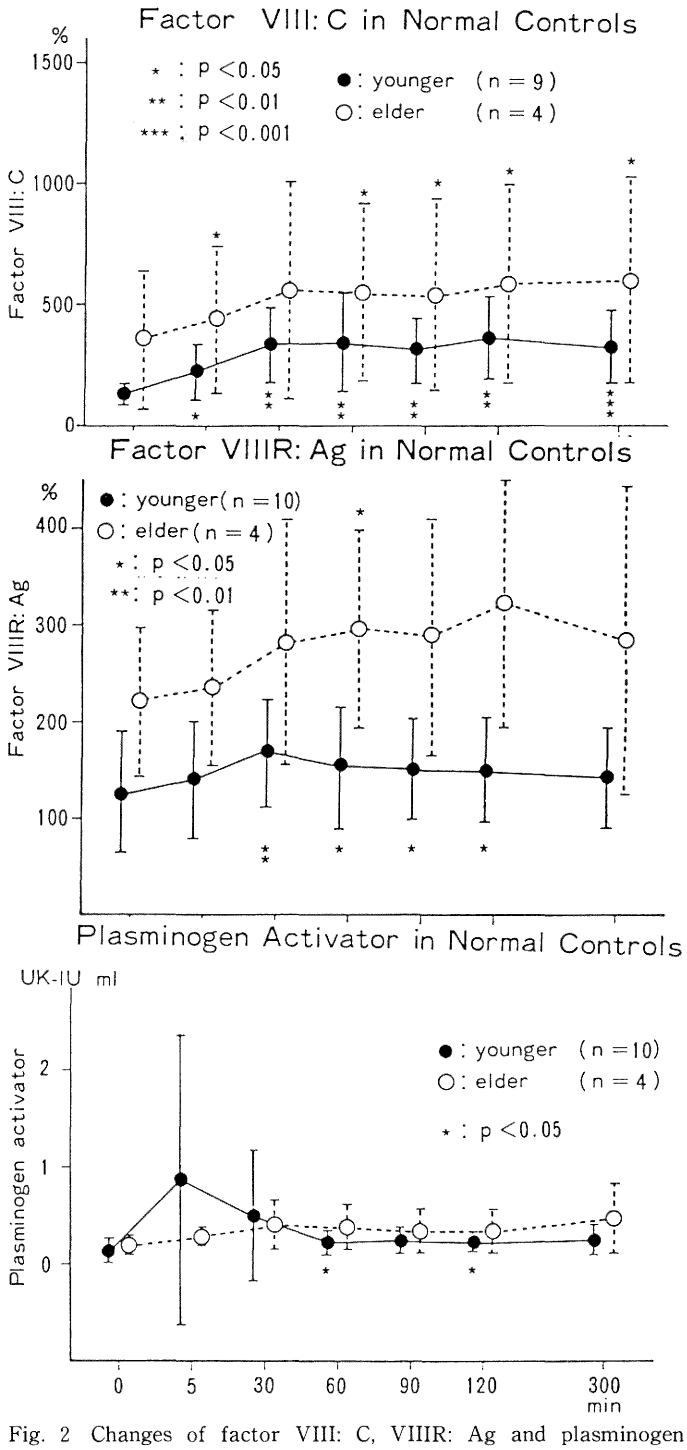

Fig. 2 Changes of factor VIII: C, VIIIR: Ag and plasminogen activator after injection of 4 μg of DDAVP in the both younger and elder groups.

min in the cases of 8 μg DDAVP injection and in the younger group (Fig. 1 and 2).

(2) Injection of 8 μg of DDAVP to patients:

Case 1: T. M. 18 year old male. Clinical diagnosis: Cerebral thrombosis of the basilar artery. Past history: In 1983, he was diagnosed to have essential hypertension, and epistaxis was observed frequently. Family history: No disposition of thromboembolism and haemorrhagic tendency. Present history: Jan. 21, 1983, he complained of a severe headache and was admitted to Kuwana Hospital in a comatic state. Anisocoria was observed (left side>right side), midriatic light reflex were gone out, and eyeballs had moved to the right side. Blood pressure was 110/64 mmHg. Pulse: regular 78/min. Laboratory findings on admission: Urinalysis, and coprology were normal. Blood chemistry showed normal values in all. Haematological analysis showed a slight increase of granulocytes. The results of the coagulation studies were as follows: fibrinogen; 460 mg/dl, euglobulin lysis time; 900 min, plasminogen-activator; 0.069 IU/ml, factor VIII: C; 281 %, factor VIIIR: Ag; 185 %, α_2-macroglobulin; 264 % and α_1-antitrypsin; 335 %. Plasminogen activator showed a decrease to approximately 10 % of the normal level, euglobulin lysis time showed a slight prolongation and others showed remarkable increases. Platelet aggregation tests were normal.

Even though the plasminogen activator level is low in this case, when 8 μg of DDAVP was injected intravenously to the patient, plasminogen activator activity increased from 0.069 U to 0.35 U/ml at 30 min after the injection, and continued at that level for 90 min. Initial level of factor VIII: C was 281 % and that of factor VIIIR: Ag was 185 %. They were rather high level than normal. When 8 μg of DDAVP was injected intravenously, factor VIII: C increased to 437 % at 90 min, and factor VIIIR: Ag to 311 % at 60-90 min after injection (Fig. 3).

As mentioned above, in this case, factor VIII: C level was 3 times as high as in the normal controls; on the contrary, plasminogen activator level was only 10 % of normal. These values might have some relation to the occurrence of cerebral thrombosis in this young patient who had no underlying disease leading to the thrombotic tendency. APTT shortened concomitant with the increase of factor VIII: C from 29.0 to 25.5 sec. The presence of the active enzymes such as thrombin or factor Xa in plasma makes the aPTT shortened. In this case, however, no activity of such active enzymes was detected through the chromogenic substrate assay method mentioned above, and silicon PTT did not show the shortening. On the other hand euglobulin lysis time shortened from 900 to 420 min, and plasminogen decreased from 15.2 mg/dl to 14.4 mg/dl. A decrease in α_2-plasmin inhibitor (α_2-Pl, assayed by using chromogenic substrate: S-2251, Kabi Co) was observed. These findings suggest that the fibrinolytic system was not activated much by the injection of DDAVP.

Case 2: Father of the patient was 48 years old. 8 μg of DDAVP was injected intravenously, and coagulation-fibrinolytic studies were performed. Factor VIII: C increased from 140 to 340 %, and aPTT shortened from 24.5 to 21.5 sec. Plasminogen

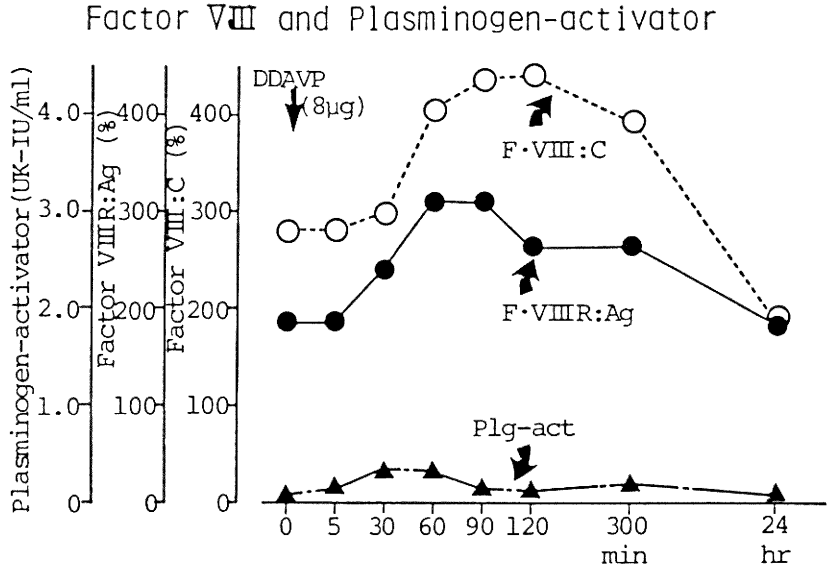

Fig. 3 Case 1. T. M. 18 years old, male. Changes of factor VIII: C and plasminogen activator after injection of 8 μg of DDAVP.

activator increased from 0.68 to 4.85 U/ml, and the euglobulin lysis time shortened remarkably from 410 to 50 min. Other coagulation-fibrinolytic factors did not change significantly.

Case 3: Mother of the patient was 48 years old. 8 μg of DDAVP was injected intravenously. In this case also factor VIII: C increased ramarkably from 220 to 900 %, and aPTT shortened from 25.4 to 22.9 sec. Plasminogen activator increased from 0.37 to 4.30 U/ml similar to case 2, and the euglobulin lysis time also shortened from 370 to 30 min. Other coagulation-fibrinolytic factors did not change.

(3) Fibrinolytic therapy

Fibrinolytic therapy using urokinase was performed on this 18 year old patient who showed poor response to DDAVP. 180,000 units of urokinase per day was injected intravenously for 4 days. Euglobulin lysis time did not change remarkably, but plasminogen decreased from 12.0 to 8.2 mg/dl. The inhibitor of fibrinolysis, i. e, α_2-PI did not change significantly (Fig. 4). There was no improvement in the clinical symptoms. Angiography and CT scanning were repeated after injection of urokinase, and no change was found in them.

Thrombolytic therapy, using urokinase, was also performed on the patient who showed a good response to DDAVP.

Case 4: She was 75 years old and had right middle-cerebral artery occlusion. She was injected 8 μg of DDAVP intravenously, and found to have high response of both plasminogen activator and factor VIII: C (Fig. 5). To this patient, 180,000 units of urokinase per day was injected intravenously for 4 days. The fibrinolytic activity

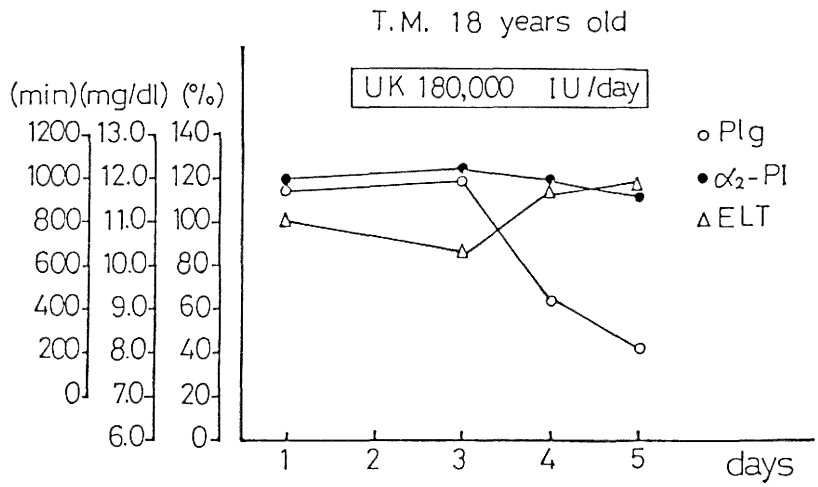

Fig. 4 Case 1. T. M. 18 years old, male. Changes of α_2-plasmin inhibitor, euglobulin lysis time and plasminogen after injection of 180, 000 units of urokinase.

increased remarkably, which was shown by the shortening of the euglobulin lysis time, and the decrease of plasminogen and α_2-PI. Improvement of clinical symptom, angiographic and CT-scanning findings were observed after the injection of urokinase (Fig. 6).

DISCUSSION

An 18-year-old young patient with cerebral thrombosis has been reported. Cerebral thrombosis in young individuals is known to be caused by some coagulation disorders which induce a hypercoagulable state. We previously reported on a case of cerebral

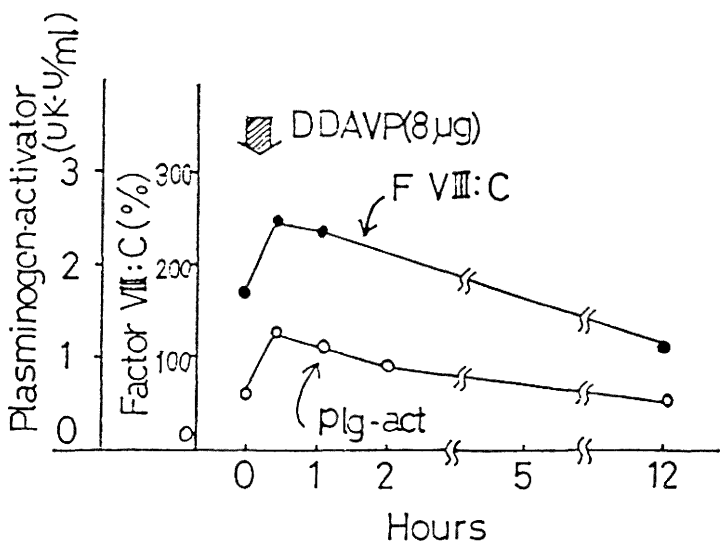

Fig. 5 Case 4. F. O. 75 years old, female. Changes of factor VIII: C and plasminogen activator after injection of 8 μg of DDAVP.

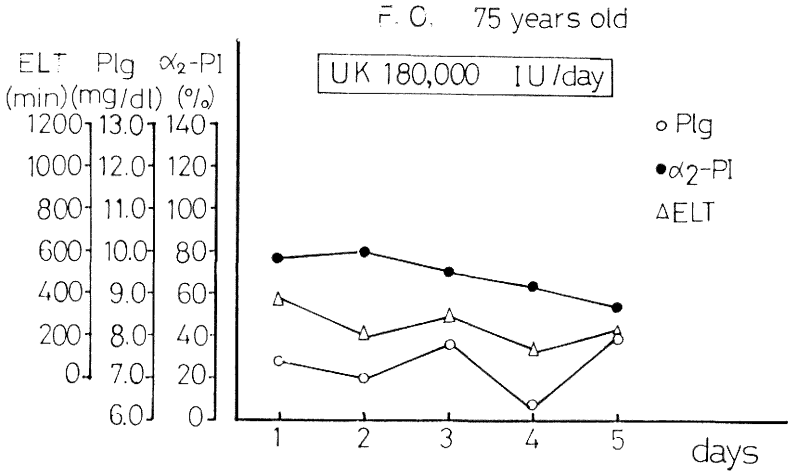

Fig. 6 Case 4. F. O. 75 years old, female. Changes of α_2-plasmin inhibitor, euglobulin lysis time and plasminogen after injection of 180,000 units of urokinase.

thrombosis in which abnormal antithrombin III (antithrombin III "Toyama") was discovered (4). The patient's antithrombin III showed no affinity to heparin, and no immediate inhibitory effect on thrombin because of the replacement of 47-Arg to Cys in its amino acid sequence. In Moyamoya disease, on the other hand, cerebral thrombosis is a well-known complication in young patients (8). Some collagen diseases and heart diseases also may accompany ischemic disorders in the central nervous system. In our case, however, these underlying diseases were not found at all. Concerning DDAVP, many reports say that a dose of 0.3-0.4 μg/kg will be enough for the release of factor VIII and plasminogen activator from the vessel wall (5, 6). We found, however, that even smaller doses are effective for the release of factor VIII and plasminogen activator. The only abnormality found in our case was the very low level of plasminogen activator and the high level of factor VIII: C after exploratory intravenous injection of DDAVP: therefore his blood vessel walls were evaluated to be abnormally hypercoagulable and hypofibrinolytic. Abnormally low release of plasminogen activator from the vessel wall may induce ischemic disorders in the central nervous system in individuals, because this activity appears to play an important role in the inhibition of thrombus formation of the vessel wall. Moreover, fibrinolytic activity of the vessel wall seems to have some supportive effect on the thrombolytic therapy using urokinase, since in our fourth case showing a high level of plasminogen activator by DDAVP injection, a good response to urokinase therapy was observed.

We could not estalbish whether this abnormality in our first case was hereditary or not, although some groups have already reported about the high incidence of recurrent thrombosis in families with a low release of plasminogen activator from the vessel wall by DDAVP injection.

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