

Expression and significance of vWF, GMP-140 and ADAMTS13 in patients with aneurysmal subarachnoid hemorrhage

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Abstract. – **OBJECTIVE:** The aim of this study was to investigate the role of the von Willebrand factor (vWF) in patients with aneurysmal subarachnoid hemorrhage (aSAH), platelet membrane glycoprotein-140 (GMP-140). The aim is also to discover the expression and clinical significance of von Willebrand factor (vWF) cleaving protease (ADAMTS13).

PATIENTS AND METHODS: 83 patients with aSAH were selected from January 2014 to December 2016. The patients were divided into cerebral vasospasm group (CVS group) (n = 37) and no convulsion group (non-CVS group) (n = 46); delayed cerebral ischemia group (DCI group) (n = 31) and non-delayed cerebral ischemia group (non-DCI group) (n = 52). Also, the different aneurysm diameter group included 43 patients in < 5 mm group, 29 patients in 5-10 mm group, 11 patients in > 10 mm group. The number of patients in the good prognosis group and the poor prognosis group were 49 and 34, respectively. Enzyme-linked immunosorbent assay (ELISA) was used to detect the levels of vWF, GMP-140, and ADAMTS13 in plasma of aSAH patients, and the correlation between the indexes was analyzed.

RESULTS: The repeated measures analysis of variance showed that there was no significant difference in plasma vWF, GMP-140, and ADAMTS13 levels in each group of the aSAH patients ($p < 0.05$). The vWF level of the CVS group was higher than that of the non-CVS group on day 4 and day 10. The GMP-140 level of the CVS group was higher than that of the non-CVS group on day 1, day 4 and day 10. And the ADAMTS13 level was lower than that of the non-CVS group on day 1 and day 10. The difference was statistically significant ($p < 0.05$). The plasma vWF level of DCI group was higher than that of the non-DCI group on day 1 and day 4. The plasma GMP-140 level at day 4 was higher than that of the non-DCI group. The plasma ADAMTS13 level at day 1 was lower than that in the non-DCI group. The difference was significant ($p < 0.05$). The plasma vWF level in >

10 mm group was higher than that in < 5 mm group and 5-10 mm group at day 1 and day 4. The plasma vWF level in 5-10 mm group was higher than that in < 5 mm group at day 4. The plasma GMP-140 levels in > 10 mm group were higher than that in < 5 mm group and 5-10 mm group at day 1 and day 4. The plasma GMP-140 level in 5-10 mm group was higher than that in < 5 mm group at day 1. The plasma ADAMTS13 level in > 10 mm group was lower than that in < 5 mm group and 5-10 mm group on day 1. Moreover, the plasma ADAMTS13 level in 5-10 mm group was lower than that in < 5 mm group: $p < 0.05$. The plasma vWF level in the good prognosis group was lower than that in the poor prognosis group on day 4 and day 10. On day 1, day 4, and day 10, the level of GMP-140 was lower than that of the poor prognosis group. The ADAMTS13 level on day 1 and day 4 was higher than that in the poor prognosis group. The difference was statistically significant ($p < 0.05$). Pearson product moment correlation analysis showed that the plasma vWF level was positively correlated with GMP-140 at day 1 ($r = 0.334$, $p < 0.05$), negatively correlated with ADAMTS13 ($r = -0.426$, $p < 0.05$), and GMP-140 was negatively correlated with ADAMTS13 ($r = -0.398$, $p < 0.05$). At day 4, plasma vWF was positively correlated with GMP-140 ($r = 0.278$, $p < 0.05$), negatively correlated with ADAMTS13 ($r = -0.311$, $p < 0.05$), and GMP-140 was negatively correlated with ADAMTS13 ($r = -0.235$, $p < 0.05$). At day 10, there was no significant correlation between vWF, GMP-140, and ADAMTS13 ($p > 0.05$).

CONCLUSIONS: VWF, GMP-140, and ADAMTS13 were correlated with the diameters and prognoses of CVS, DCI, aneurysms. Combined detection can help to evaluate the condition of patients with aSAH, so as to provide a guide for clinical treatment and prognosis.

Key Words:

Aneurysmal subarachnoid hemorrhage, Von Willebrand factor, gmp-140, ADAMTS13.

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a medical emergency, due to the rupture of an aneurysm. In general, aSAH causes the blood from the rupture of intracranial blood vessels to flow into the subarachnoid space¹. aSAH has high morbidity and mortality rate in the middle age and elderly after hypertensive intracerebral hemorrhage^{2,3}. Previous researches⁴ showed that nearly 50% of aSAH patients died after onset for 24 h. It is important to improve the prognosis of patients by evaluating the condition of aSAH at an early stage and taking targeted interventions. Von Willebrand factor (vWF) is an important protein in normal coagulation process of human body. Overexpression of vWF can promote platelet aggregation and accelerate the formation of thrombus^{5,6}. It has been reported that⁷ plasma vWF antigen is closely related to cerebral infarction and myocardial infarction. Platelet granule membrane protein-140 (GMP-140) is a specific molecular marker of platelet activation and participates in the pathophysiology of thrombosis⁸. Von Willebrand factor cleaving protease (ADAMTS13) is a kind of metalloproteinase, synthesized mainly in the liver. It degrades the vWF and reduces the formation of thrombus. A research has shown that⁹ the decrease of ADAMTS13 activity and the increase of vWF antigen may increase the risk of cerebral infarction. In this study, vWF, GMP-140 and ADAMTS13 levels in plasma of patients with aSAH were dynamically monitored in order to explore the correlation between the progression and prognosis of the aSAH patients.

Patients and Methods

Patients

83 cases of aSAH patients were collected in our hospital (Affiliated Hospital of Qinghai University, Xining, Qinghai, China) from January 2014 to December 2016 as the experimental group.

Inclusion criteria: (1) patients who had lumbar puncture or subarachnoid hemorrhage at admission; (2) CTA or DSA examination confirmed that the SAH of patients was caused by rupture of intracranial aneurysm; (3) the patients ranged from 18-75 years old; (4) patients who had aneurysm clipping operation previously.

All patients or family members have signed the informed consent. This study was approved by the Ethical Committee of Qinghai University.

Exclusion criteria: (1) women who were in pregnancy and lactation; (2) patients who had liver and kidney dysfunction; (3) patients who had cardiac insufficiency; (4) the SAH of patients which were caused by infection and trauma; (5) at the time of admission, the onset time was more than 72 h or dying patients; (6) patients who were taking anticoagulants such as warfarin, or antiplatelet drugs such as aspirin; (7) patients who had infectious diseases.

There were 45 male patients and 38 female patients, age range of 37-75 years old (59.83 ± 4.67). There were 43 cases < 5 mm of the aneurysm diameters, 29 cases 5-10 mm, 11 cases > 10 mm. There were 21 cases of anterior communicating artery aneurysm, 13 cases internal carotid artery aneurysm, 17 cases internal carotid posterior communicating artery aneurysm, 19 cases anterior cerebral artery aneurysm, 8 cases middle cerebral artery aneurysm and 5 cases posterior cerebral artery aneurysm. There were 23 cases II grade in Hunt-Hess grade (10) system, 12 cases III grade, 10 cases IV grade, 8 cases V grade.

According to the diagnostic criteria of cerebral vasospasm, patients were divided into two groups with 37 patients in cerebral vasospasm group (CVS group) and 46 patients in non-spasm group (non-CVS group). According to the diagnostic criteria of delayed cerebral ischemia, 31 patients were divided in delayed cerebral ischemia group (DCI group) and 52 patients were in non-delayed cerebral ischemia group (non-DCI group). According to the different diameters of aneurysm, 43 patients were in < 5 mm group, and 29 patients were in 5-10 mm group, and 11 were in > 10 mm group. According to the prognosis, 49 patients had good prognosis, and 34 patients had bad prognosis. For the diagnostic criteria for cerebral vasospasm¹¹, the ultrasound results showed that the mean velocity of middle cerebral artery was > 120 cm/s in the patients during 3-14 days after admission. The mean cerebral blood flow velocity index (Lindgaard) of ipsilateral middle cerebral artery and internal carotid artery was > 3 . The diagnostic criteria for delayed cerebral ischemia¹² was as follows: (1) emerging local neurological dysfunction; (2) cerebral infarction; (3) Glasgow coma scale (GCS) decreased > 2 ; (4) exclusion of obstructive hydrocephalus and intracranial re-bleeding. For prognostic grouping criteria¹³, we used the Glasgow outcome scale (GOS) to evaluate the patients discharged from hospital, which is 1 point for death, 2 points for vegetative status, 3 points for severe disability, 4 for mild disability,

and 5 for full recovery. 4 and 5 were judged as good prognosis, and 1, 2, 3 were judged as poor prognosis.

Methods

On day 1, day 4 and day 10 after admission, 5 ml fasting venous blood was collected, and added into a citrate anticoagulation tube. The blood was centrifuged at speed 3000 r/min for 10 min, and the plasma was collected and preserved at -80 °C. Enzyme linked immunosorbent assay (ELISA) was used to measure the levels of vWF, GMP-140 and ADAMTS13 in plasma of each group. VWF, GMP-140, ADAMTS13 kits were purchased from Sichuan MEIKO Bio Polytron Technologies Inc. (Chengdu, Sichuan, China). All operations were in strict accordance with the instructions on the kit.

Outcome Measures

The plasma levels of vWF, GMP-140 and ADAMTS13 were dynamically monitored on day 1, day 4 and day 10 after admission.

Statistical Analysis

All data in this study were recorded and analyzed by SPSS19.0 software. Description of quantitative data was represented by ($\bar{x} \pm s$). ANOVA was used to compare the repeated measurement data, and followed by *t*-test. The qualitative data was described by the ratio (%), and the correlation between each index was analyzed by Pearson product moment correlation.

Results

Dynamic Changes of vWF, GMP-140 and ADAMTS13 levels in CVS Group and aSAH Group Without CVS

The analysis of repeated measurements of variance showed that, there was no significant difference of the plasma vWF, GMP-140, ADAMTS13 levels of aSAH patients in CVS group and non CVS group ($p > 0.05$). The vWF level of CVS group was higher than that of non CVS group on day 4 and day 10, and the difference was statistically significant ($p < 0.05$). The GMP-140 level of CVS group was higher than that of non CVS group on day 1, day 4, and day 10, and the difference was statistically significant ($p < 0.05$). The ADAMTS13 level of CVS group was lower than that of non CVS group on day 1 and day 10, and the difference was statistically significant ($p < 0.05$), as shown in Table I.

Dynamic Changes of vWF, GMP-140 and ADAMTS13 Levels in DCI group and non DCI Group Patients with aSAH

There was no significant difference in plasma vWF, GMP-140 and ADAMTS13 levels of aSAH patients in DCI group and non DCI group ($p > 0.05$). The plasma vWF level in group DCI was higher than that in non DCI group in day 1, and ADAMTS13 level was lower than that in non DCI group ($p < 0.05$). The plasma vWF and GMP-140 level in day 4 were higher than those in non DCI group ($p < 0.05$), as shown in Table II.

Table I. Dynamic changes of vWF, GMP-140 and ADAMTS13 levels in CVS group and aSAH group without CVS.

Group	Case	Day 1			Day 4			Day 10		
		vWF (U/ml)	GMP-140 (ng/ml)	ADAMTS13 (%)	vWF (U/ml)	GMP-140 (ng/ml)	ADAMTS13 (%)	vWF (U/ml)	GMP-140 (ng/ml)	ADAMTS13 (%)
CVS	37	2.89±1.02	51.22±17.60*	51.24±20.67*	3.64±1.15*	46.29±18.65*	59.06±21.24	3.79±0.98*	39.37±16.99*	53.45±20.89*
Non-CVS	46	2.11±1.17	34.48±18.57	62.34±19.85	2.53±1.09	35.97±17.61	63.35±20.09	1.76±1.00	21.52±18.78	66.98±21.04

Note: Compared with non-CVS, * $p < 0.05$

Table II. Dynamic changes of vWF, GMP-140 and ADAMTS13 levels in DCI group and non DCI group patients with aSAH.

Group	Case	Day 1			Day 4			Day 10		
		vWF (U/ml)	GMP-140 (ng/ml)	ADAMTS13 (%)	vWF (U/ml)	GMP-140 (ng/ml)	ADAMTS13 (%)	vWF (U/ml)	GMP-140 (ng/ml)	ADAMTS13 (%)
DCI	31	3.37±1.68*	60.56±15.58	32.05±79±14.56*	5.29±1.53*	36.78±16.63*	56.32±15.59	3.41±1.62	28.85±15.56	46.93±16.11
Non-DCI	52	2.19±1.50	49.97±16.65	64.38±15.52	2.24±1.66	29.90±16.03	57.86±14.55	3.35±1.59	26.60±15.92	51.58±15.61

Note: Compared with non-CVS, * $p < 0.05$

Table III. Dynamic changes of vWF, GMP-140 and ADAMTS13 levels in patients with different diameters of aneurysm aSAH ($\bar{x} \pm s$).

Group	Case	Day 1			Day 4			Day 10		
		vWF (U/ml)	GMP-140 (ng/ml)	ADAMTS13 (%)	vWF (U/ml)	GMP-140 (ng/ml)	ADAMTS13 (%)	vWF (U/ml)	GMP-140 (ng/ml)	ADAMTS13 (%)
<5 mm group	43	1.58±0.79	37.11±15.59	56.44±15.78	1.66±0.82	32.26±15.08	62.23±16.21	2.96±0.88	29.95±16.73	60.18±16.29
5-10 mm group	29	1.72±0.83	50.02±16.38*	38.59±16.02*	2.79±0.81*	34.41±16.02	60.02±16.46	3.12±0.79	30.13±15.98	58.83±16.19
>10 mm group	11	4.12±0.86**	62.75±16.16**	29.97±15.18**	6.01±0.77**	45.09±16.65**	57.60±16.29	3.05±0.83	31.22±16.57	56.18±15.97

Note: Compared with < 5 mm, * $p < 0.05$; Compared with 5-10 mm, ** $p < 0.05$.

Table IV. Dynamic changes of vWF, GMP-140 and ADAMTS13 levels in patients with good prognosis and bad prognosis in aSAH ($\bar{x} \pm s$).

Group	Case	Day 1			Day 4			Day 10		
		vWF (U/ml)	GMP-140 (ng/ml)	ADAMTS13 (%)	vWF (U/ml)	GMP-140 (ng/ml)	ADAMTS13 (%)	vWF (U/ml)	GMP-140 (ng/ml)	ADAMTS13 (%)
good prognosis	49	3.37±1.20	33.08±15.89*	67.30±13.38*	2.03±0.97*	27.96±14.25*	59.92±14.41*	2.58±1.19*	20.23±16.28*	52.25±15.57
Bad prognosis	34	3.69±1.08	66.24±16.72	42.69±15.11	3.95±1.15	44.02±15.00	47.06±14.97	3.87±1.23	52.15±14.61	46.19±13.98

Note: Compared with bad prognosis group, * $p < 0.05$.

Dynamic Changes of vWF, GMP-140 and ADAMTS13 levels in Patients with Different Diameters of Aneurysm aSAH

There was no significant difference in the levels of plasma vWF, GMP-140 and ADAMTS13 of patients with different diameters of aneurysm aSAH ($p > 0.05$). The plasma vWF and GMP-140 levels in > 10 mm group were higher than those in < 5 mm group and 5-10 mm group at day 1 and day 4. The plasma GMP-140 level at day 1 and the vWF levels at day 4 in the 5-10 mm group were higher than those in the < 5 mm group, the difference was statistically significant ($p < 0.05$). In > 10 mm group at day 1, the plasma ADAMTS13 level was lower than < 5 mm group and 5-10 mm group. The plasma ADAMTS13 levels of 5-10 mm group were lower than that of < 5 mm group, the difference was statistically significant ($p < 0.05$), as shown in Table III.

Dynamic Changes of vWF, GMP-140 and ADAMTS13 Levels in aSAH Patients with Good Prognosis and Bad Prognosis

There was no significant difference in the levels of vWF, GMP-140 and ADAMTS13 in plasma of patients with good prognosis and poor prognosis

in patients with aSAH ($p > 0.05$). The plasma vWF level of good prognosis group was lower than in the bad prognosis group on day 4 and day 10. The difference was statistically significant ($p < 0.05$). The GMP-140 level in good prognosis group was lower than in the bad prognosis group on day 4 and day 10, the difference was statistically significant ($p < 0.05$). The ADAMTS13 level in the good prognosis group was higher than that in the bad prognosis group on day 1 and day 4, the difference was statistically significant ($p < 0.05$), as shown in Table IV.

Correlation Analysis of Plasma vWF, GMP-140 and ADAMTS13 in Patients with aSAH

The correlation between plasma vWF, GMP-140 and ADAMTS13 in patients with aSAH was analyzed by Pearson product moment correlation. Results showed that, on day 1, plasma vWF was positively correlated with GMP-140 ($r = 0.334, p < 0.05$), negatively correlated with ADAMTS13 ($r = -0.426, p < 0.05$). There was a negative correlation between GMP-140 and ADAMTS13 ($r = -0.398, p < 0.05$). On day 4, plasma vWF was positively correlated with GMP-140 ($r = 0.278, p < 0.05$),

and negatively correlated with ADAMTS13 ($r = -0.311, p < 0.05$). There was a negative correlation between GMP-140 and ADAMTS13 ($r = -0.235, p < 0.05$). On day 10, there was no significant correlation among vWF, GMP-140 and ADAMTS13 ($p > 0.05$).

Discussion

In general cases, aSAH occurs in artery bifurcation at the Willis arterial ring surroundings. The pathological changes include hemorrhage caused by cerebral infarction, obstructive hydrocephalus, cerebral vasospasm and brain damage¹⁴. The clinical manifestations of aSAH include nausea, irritability, headache, epilepsy, hemiplegia and low back pain, which seriously affect the health and quality of daily life¹⁵. The mortality rate is as high as 45%, and postoperative complications often appear to various degrees, such as DCI, CVS, etc.¹⁶. vWF is a polysaccharide protein derived from platelet α granule and vascular endothelial cell. The regulation of vWF is mediated by the adhesion of collagen through platelets and vascular endothelial cells. Reports has been found¹⁷ that the greater the molecular weight of vWF, the stronger the binding ability between the platelet and collagen, and the more easily it can lead to the abnormal aggregation of platelet and the damage of endothelial cells. Previous researches¹⁸ showed that the vWF levels were elevated at 72 h after onset. GMP-140 is a platelet cell adhesion receptor released after platelet activation. Under normal circumstances, the body content of GMP-140 is relatively low. When the platelet is activated, GMP-140 enters the plasma and accelerates the activation and rupture of platelets. Studies have shown that¹⁹, the cerebral microvascular injury exposes the endothelium to collagen, then activates the platelets to cause the release of GMP-140. ADAMTS13, as a metalloprotease mainly synthesized in liver, functions on the peptide bond between the 842 nd tyrosine and the 843 nd methionine of vWF. ADAMTS13 also degrades vWF and reduces thrombosis^{20, 21}.

The study has found that²², CVS occurred in 70% of the aSAH patients. However, CVS is an important factor of the cause of cerebral infarction and bad prognosis. The results of this study showed that the plasma vWF, GMP-140 and ADAMTS13 levels of aSAH patients of CVS

group and non CVS group did not increase or decrease significantly along with time. However, the vWF level of CVS group was higher than that of non CVS group on day 4 and day 10. On day 1, day 4, and day 10, the GMP-140 level was higher than that of the non CVS group. The ADAMTS13 level on day 1 and day 10 was lower than that of non CVS group. It was due to the damage of endothelial cells and the activation of platelets in CVS, which indicated that VWF, GMP-140, ADAMTS13 can be considered as important indicators to diagnosis of CVS.

In this study, the levels of vWF, GMP-140, and ADAMTS13 of aSAH patients in DCI group and non DCI group were not significantly increased or decreased. However, the plasma vWF level of DCI group was higher than that of non DCI group on day 1 and day 4. The plasma level of GMP-140 on day 4 was higher than that of non DCI group. The plasma ADAMTS13 level on day 1 was lower than that of non DCI group. It was due to the decrease of plasma ADAMTS13 level in aSAH patients, which led to the incapability of degradation of vWF into small molecular fragments. vWF poly-aggregates were formed in the blood vessels to cause micro thrombosis, also elevated the levels of vWF antigen during pregnancy. At the same time, the activation of endothelial cells in DCI increased the vWF. The results showed that vWF, GMP-140, and ADAMTS13 had clinical significance in diagnosing DCI. The greater the aneurysm diameter, the worse the aSAH patients, and the worse prognosis. The results showed that there were no significant changes in plasma vWF, GMP-140 and ADAMTS13 levels in different diameters of aneurysm. However, with the increase of tumor diameter, the higher the plasma vWF and GMP-140 level, the lower of the ADAMTS13 level. It suggested that the plasma vWF, GMP-140 and ADAMTS13 were closely related to tumor diameter, the greater the diameter of the tumor, the more severe of vascular endothelial injury. Therefore, vWF, GMP-140, ADAMTS13 can be used as the index to determine the degree of vascular endothelial injury, and then assess the prognosis of aSAH patients. In addition, the plasma vWF level of the good prognosis group was lower than that of the bad prognosis group on day 4 and day 10. On day 1, day 4, and day 10, the level of GMP-140 was lower than that of the bad prognosis group. The ADAMTS13 level on day 1 and day 4 was higher than that in bad prognosis group. It in-

licated that vWF, GMP-140 and ADAMTS13 can predict the prognosis of aSAH patients and provide important clinical value. Pearson product moment correlation analysis showed that in aSAH patients on day 1, the plasma vWF was positively correlated to GMP-140, and negatively correlated with ADAMTS13, GMP-140 was negatively correlated with ADAMTS13. On day 4, plasma vWF was positively correlated with GMP-140, and negatively correlated with ADAMTS13, and GMP-140 was negatively correlated with ADAMTS13. It meant that the levels of plasma vWF, GMP-140 and ADAMTS13 in aSAH patients can be used to evaluate the severity of the disease, and to improve the prognosis of patients.

Conclusions

To conclude, VWF, GMP-140, ADAMTS13 and the CVS, DCI, tumor diameter and prognosis of aSAH patients are closely related. It can be used as an important index to evaluate the severity of aSAH, so as to provide a guide for clinical treatment and prognosis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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