

FIBRINOLYTIC AND FACTOR XIII ACTIVITY IN SUBARACHNOID HEMORRHAGE

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ABSTRACT - The balance between fibrinolytic activity and coagulation mechanisms seems to play an important role in the rebleeding of a subarachnoid hemorrhage (SAH) due to aneurysmatic rupture. In the present paper we describe our findings in a group of patients (n10) with SAH. The plasmatic levels of fibrinogen and their degradation products (FDP), APTT, prothrombin activity and factor XIII were determined within 72 hours of initial bleeding, or of eventual rebleeding. Factor XIII activity in the first bleeding was $82.1 \pm 4\%$, while the levels of FDP were $3.8 \pm 1 \mu\text{g/ml}$. In patients presenting rebleeding (n4), Factor XIII activity was $67.3 \pm 4.5\%$ the day it manifested, which is significantly less than the values previously observed ($p < 0.01$), while the FDP level was $4.1 \pm 2 \mu\text{g/ml}$. The decrease of factor XIII activity suggests an important role as regards clot stability in rupture location. It is also possible to attribute a rebleeding predictive value to its activity reduction.

KEY WORDS: factor XIII activity, subarachnoid hemorrhage, aneurysm rebleeding.

Actividad fibrinolítica y del factor XIII en la hemorragia subaracnoidea

RESUMEN - El balance entre la actividad fibrinolítica y los mecanismos de la coagulación juegan un rol importante en el resangrado de una hemorragia subaracnoidea debido a ruptura aneurismática. En el presente estudio se describen nuestros hallazgos en un grupo de pacientes (n10) con hemorragia subaracnoidea (SAH). Los niveles plasmáticos de fibrinogeno y sus productos de degradación (FDP), la actividad de protrombina (APTT) y de factor XIII fueron determinados dentro de las 72 hs, del sangrado inicial y ante el eventual resangrado. La actividad de factor XIII en el primer sangrado fue de $82,1 \pm 4\%$, mientras el nivel de FDP fue de $3,8 \pm 1 \mu\text{g/ml}$. En aquellos pacientes que resangraron (n4), la actividad de factor XIII fue de $67,3 \pm 4,5\%$, el día del resangrado, el cual es significativamente menor que los valores previamente observados ($p < 0.01$), mientras que los niveles de FDP fueron $4,1 \pm 2 \mu\text{g/ml}$. La reducción de la actividad de factor XIII sugiere un importante rol de este en la estabilidad del coágulo en el sitio de ruptura aneurismática, siendo posible atribuir un valor predictivo a la reducción de su actividad.

PALABRAS-LLAVE: actividad de factor XIII, hemorragia subaracnoidea, resangrado aneurismático.

After subarachnoid hemorrhage (SAH) due to aneurysmatic rupture, rebleeding occurs in 20 to 25% of patients, which increases mortality rate from 55% to nearly 100%.⁰, according to admission conditions^{5,8}. Mechanisms of coagulation and fibrinolysis have been described in patients with SAH due to rupture of aneurism^{3,4,10}. Fibrinolytic activity increase has been considered an etiology of aneurysmatic rebleeding, resulting in an increment of fibrogen degradation products (FDP) in cerebrospinal fluid^{2,13}. Likewise, a reduction of fibrin stabilizing factor (Factor XIII) has been determined in SAH patients during the two first weeks after initial bleeding⁹.

In the present study we have evaluated coagulation as well as fibrinolysis in the beginning (initial bleeding) and in case of rebleeding, in a group of SAH patients.

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Table 1. Fibrinogen, FDP, APTT, PA and factor XIII dosages (mean, SD) in ten patients with subarachnoid hemorrhage due to rupture of aneurysm.

	Fibrinogen mg/dl	FDP µg/ml	APTT sec.	PA %	Factor XIII %
Initial bleeding (n:10)	365±32	3.8±1.1	28±7	75±16	82.1±4.5
Rebleeding (N:4)	346±26	4.0±2.0	43±1	79±19	67.3±4.5*

Fibrinolysis and coagulation indicators: PA, prothrombin activity; FDP, fibrinogen degradation products; APTT, activated partial thromboplastin time.

*p<0.01

SUBJECTS AND METHODS

Ten patients were observed (6 males and 4 females) with average ages of 47.5±16 who suffered SAH due to aneurysmatic rupture angiographically confirmed. Angiography and CT scan were performed in all cases.

The fibrinogen plasmatic levels (Clauss method; Q.Stago reagents), FDP (latex method; Q.Stago reagents), activated partial thromboplastin time (APTT) (cefalin-kaolin method), prothrombin activity (clotting assay; Behringwerke AG Germany reagents) and factor XIII activity (clot solubilization assay; Behringwerke AG Germany reagents) were determined.

The measurements were effected on admission and in case of rebleeding.

With those methose the ranks of normal values in our laboratory were: fibrinogen, 200 to 400 mg/dl; FDP, 2.4±1.8µg/ml; APTT, 35 to 55 seconds; prothrombin activity, 70 to 100%; and factor XIII, 95±5%.

For statistical evaluation it was used T test for paired samples.

RESULTS

The patients were clinically classified according to Hunt and Hess grading system. Seven met the requirements to be included in grades I and II, other three in grade III.

Among 10 patients, 4 bleed again within the first two weeks (8±2 days). Two of them were classified to grade II and two to grade III. One of the patients who rebleed died. The laboratory parameters (Table 1) showed an increment of FDP to 3.8±1.1 µg/ml (control value: 2.4±1.8µg/ml;

Table 2. Factor XIII activity in initial bleeding and after rebleeding in patients with aneurysmatic rebleeding.

Patients	Factor XIII activity (%)	
	Initial bleeding	Rebleeding
2	82.5	71
4	77.5	70
7	80	67.5
8	80	61
$\bar{x} \pm SD$	80.0±2.0	67.3±4.5*

*p<0.01

n10) and a reduction of factor XIII activity during the first bleeding. In those who rebleed a significant reduction (p<0.01) of factor XIII activity was observed the rebleeding day (value found in initial bleeding 80±2%, value in rebleeding 67.3±4.5% (Table 2).

DISCUSSION

Morbimortality of SAH due to aneurysmatic rupture can be lowered by reducing rebleeding^{5,6}. To achieve this end a therapeutic resource has been used to reduce fibrinolysis by means of antifibrinolytic medication. These drugs have been used in order to diminish the risks implied in a new bleeding. However, other studies have shown^{1,7,12,14} the inefficacy of these drugs in the first days after SAH.

Likewise, an increment of ischemic complications with some of the drugs utilized has been observed⁷.

Different studies have determined an increment of fibrinolytic activity, which would support the reasonableness of the therapeutics. However, another important finding is the decrease of factor XIII activity in the first weeks after bleeding^{3,4,11}.

Factor XIII catalyzes the crossed-link of fibrin with the antiplasmin alpha 2; the latter has an inhibitory effect upon fibrinolysis, as it inactivates plasmin, being therefore, an important local factor directed to avoid clot degradation in aneurysmatic rupture location.

Studies about factor XIII activity have shown that at least 70% is necessary to maintain bleeding clot stability.

Our findings show that even if fibrinolytic activity is increased, as seen in FDP levels, such value would not be significantly modified on occasion of rebleeding. The same cannot be said of factor XIII activity that is reduced to significant levels in comparison with the levels previously found.

In conclusion, factor XIII would fulfill a decisive role in clot stabilization, interacting with fibrinolysis. The significant reduction of its activity after aneurysmatic rupture might be predictive of future bleeding.

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