Factor VIII R:Ag as a prognostic parameter in intracranial haemorrhage

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SUMMARY Factor VIII R:Ag was measured serially in 42 patients who had intracranial haemorrhage. It was found that the factor decreased or remained static in the 24 patients who improved ($p < 0.025$), while it increased in the 18 who died ($p < 0.0005$). It is suggested that this factor can be used as a prognostic parameter to predict the outcome after intracranial haemorrhage.

Factor VIII circulates in the plasma as a complex composed of two components: factor VIII:C, which has the clotting activity, and factor VIII R:Ag, or von Willebrand's Factor, which is responsible for platelet adhesiveness to subendothelium.¹ Factor VIII R:Ag is synthesised mainly by endothelial cells and megakaryocytes.²⁻⁵ It is released from endothelial cells into the blood stream in response to certain stimuli, such as venous occlusion, exercise, infusion of adrenaline, nicotinic acid, vasopressin and 1-deamino-8-D arginine vasopressin (DDAVP).^{6,7} A rise in factor VIII R:Ag level is noticed after pneumoencephalography and electro-shock which is not blocked by beta blockers.^{8,9} It is also seen in glomerulonephritis, pre-eclampsia and in limb ischaemia in diabetes.¹⁰

Since all parameters used to assess the prognosis in intracranial haemorrhage are either clinical or radiological,¹¹ and since there are no chemically measurable substances to achieve this, we decided to study the value of factor VIII R:Ag in this respect. The aim was to determine the changes of factor VIII R:Ag in cases of intracranial haemorrhage and to study prospectively whether it can be used as a prognostic factor in the determination of the outcome in patients affected with such haemorrhage, and to do so as early as possible in the course of the disease.

Patients and methods

This study was prospective and concerned 62 patients who were admitted to the Jordan University Hospital (JUH) in the years 1983, 1984 and 1985. All patients with suspected CNS bleeding were subjected to computed tomography (CT) on admission, and those with proven CNS bleeding were admitted to the study. All patients were examined by the three authors daily until discharge or death, and all relevant information was thus recorded.

On admission a full "coagulation screen" was performed on each patient, and consisted of: (1) Bleeding time by the Ivy method using simplate-II device (General Diagnostics, New Jersey, USA), (2) Prothrombin time and partial thromboplastin time (Orthodiagnosics, Raritan, New Jersey, USA), (3) Plasma fibrinogen by electro-immunoassay using commercial antisera (Hoechst, Frankfurt/Main, West Germany), and (4) Manual platelet count. In addition the plasma was tested on the first and third days following admission for factor VIII R:Ag and factor VIII:C as previously described.¹²

Results

Sixty two patients were studied, 20 of whom were excluded: ten because of underlying haemostatic defect (table 1), four because of disseminated intra-

Table 1 Underlying haemostatic defect: patients excluded from the study

Haemostatic defect	No
Acquired platelet dysfunction	1
Acquired vitamin K deficiency	2
Idiopathic thrombocytopenic purpura	1
von Willebrand's disease	4
Hypofibrinogenaemia	2
Total	10

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Table 2 Causes of intracranial haemorrhage after exclusion of patients with underlying haemostatic defect

Cause	Male				Female			
	No	Dead	Alive	Age* (yr)	No	Dead	Alive	Age* (yr)
Trauma	7	3	4	52.4	2	1	1	30.5
Hypertension	10	6	4	53.7	7	4	3	47.9
Primary	5	1	4	25.3	6	2	4	29.1
Aneurysmal	2	1	1	20.5	3	0	3	35.2
Total	24	11	13	44.6	18	7	11	37.6

*Mean.

Table 3 The values of factor VIII R:Ag in the first group (alive) as measured on day 1 and day 3 post ictus

Patient No	R:Ag value* (Day 1)	R:Ag value* (Day 3)	Patient No	R:Ag value* (Day 1)	R:Ag value* (Day 3)
1	520	520	13	200	134
2	680	580	14	250	134
3	218	180	15	246	130
4	520	420	16	194	115
5	412	412	17	600	480
6	420	360	18	339	259
7	150	150	19	412	332
8	534	160	20	460	382
9	450	450	21	400	325
10	750	450	22	360	275
11	400	300	23	220	141
12	225	225	24	250	175

*Percent of normal.

Mean $\pm$ SD (Day 1): 383.75 $\pm$ 161.95Mean $\pm$ SD (Day 3): 295.38 $\pm$ 142.37

p < 0.025

Table 4 The values of factor VIII R:Ag in the second group (dead) as measured on day 1 and day 3 post ictus

Patient No	R:Ag value* (Day 1)	R:Ag value* (Day 3)	Patient No	R:Ag value* (Day 1)	R:Ag value* (Day 3)
1	520	750	10	160	250
2	420	550	11	330	630
3	200	620	12	254	354
4	360	550	13	200	286
5	400	800	14	312	522
6	412	612	15	250	460
7	360	548	16	235	445
8	400	525	17	200	410
9	360	630	18	303	516

*Percent of normal.

Mean $\pm$ SD (Day 1): 315.33 $\pm$ 97.44Mean $\pm$ SD (Day 3): 525.44 $\pm$ 144.02

p < 0.0005

vascular clotting (DIC), and six because of sampling error. Of the remaining 42 patients 24 were males (mean age 44.63 years $\pm$ 20.13 SD) and 18 females (mean age 37.58 years $\pm$ 17.36 SD). The causes of bleeding are shown in table 2. We divided the patients into two prognostic categories: alive and dead (hereafter called group 1 and group 2 respectively).

Factor VIII R:Ag values on admission in group 1 varied between 150% and 750% (normal 100%) with a mean of 383.75 and SD $\pm$ 161.95, and on day three it varied between 115% and 550% with a mean of

295.38 and SD $\pm$ 142.37, (table 3). In group 2 the values varied on admission between 160% and 520% with a mean of 315.33 and SD $\pm$ 97.44 and on the third day they varied between 250% and 800% with a mean of 525.44 and SD $\pm$ 144.02, (table 4).

It can be seen clearly from figs 1 and 2 that there was a significant decline in the factor VIII R:Ag values for the first group between day one and three (p < 0.025), whereas there was a significant rise in the factor VIII R:Ag values for the second group between day one and day three (p < 0.0005).

Fig 1 The variation in the values of factor VIII R:Ag between day one and day three in group 1 ($p < 0.025$).

Discussion

Since all available parameters used as prognostic indicators in intracranial haemorrhage are either clinical or radiological,¹¹ we aimed at identifying a chemically measurable substance that would predict prognosis in this common disease early in its course, rather than wait for longer periods awaiting changes in the clinical status of the patient or subjecting him to repeated investigations.

Factor VIII R:Ag was selected as a potential substance because: (1) it is synthesised by the vascular

endothelium,²⁻⁵ (2) it is known to increase after many CNS insults,⁶⁻⁹ (3) it is easily measured with a half life of 12 hours.

We found that factor VIII R:Ag decreased or remained static in all those who showed clinical improvement ($p < 0.025$) irrespective of their initial presenting clinical condition, whereas it increased in all those who died ($p < 0.0005$), again irrespective of their initial clinical status. It is suggested that the increase in factor VIII R:Ag values indicates a continuous or repeated endothelial injury or stimulation reflecting a continuous or repeated CNS damage. It is suggested that the decrease in factor VIII R:Ag values indicates a cessation of the endothelial injury or stimulation reflecting an arrest of the CNS insult.

In spite of the statistical significance of the results, we recognise that the patient population is rather small and the study on a larger number of patients is necessary.

It is interesting to note that 10 out of the 62 patients had an underlying haemostatic defect as a cause of their CNS bleeding, a point that emphasises our previous finding in this respect.¹³ It is suggested that all patients with intracranial haemorrhage should have a coagulation study performed as part of their management.

We conclude that the serial measurement of factor VIII R:Ag is a useful new tool in predicting the prognosis in patients affected with intracranial haemorrhage.

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Fig 2 The variation in the values of factor VIII R:Ag between day one and day three in group 2 ($p < 0.0005$).

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