Acta Neurochir (Wien) (1997) 139: 319–324

Acta Neurochirurgica

Printed in Austria

Platelet Derived Growth Factor and Subarachnoid Haemorrage: A Study on Cisternal Cerebrospinal Fluid

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Summary

Platelet derived growth factor (PDGF) was identified as a powerful mitogenic growth factor which is released from activated platelets and has a marked activity as vasoconstrictor agent. In the present study we have measured cisternal cerebrospinal fluid (CSF) levels of PDGF in 72 patients operated on for intracranial aneurysm in order to verify whether it might be related to the clinical aspects of SAH with special regard to symptomatic vasospasm.

CSF samples were obtained at surgery by cisternal puncture of the subarachnoid cistern the nearest to the aneurysm before aneurysm isolation and exclusion. The specimen were frozen in liquid nitrogen and stored at –80° C until analysis. PDGF was measured using a commercially available reagent. Values are expressed as pg/ml of CSF.

In 18 cases no radiological and clinical signs of SAH were detected and the mean cisternal CSF level of PDGF was 885.0±104.5 pg/ml; 20 patients were operated on between day 1 and 3 from the last SAH episode: mean cisternal CSF level of PDGF was 1917.5±459.4 pg/ml. In 34 patients treated with delayed surgery protocol, mean cisternal CSF level of PDGF was 995.3±73.8 pg/ml. Statistical analysis showed significant differences between groups (P: 0.011). In the subgroup of patients operated on within day 3 after SAH, 6 presented vasospasm and had mean cisternal CSF PDGF level which was significantly higher ($P<0.01$) than in 14 patients without vasospasm. In the delayed "surgical" patients there was no significant difference in cisternal CSF levels of PDGF considering the occurrence of vasospasm.

The results of the present study suggest that (a) after SAH there is a significant release of PDGF early after SAH and (b) higher levels of PDGF found in cisternal CSF of patients operated on within 72 hours after SAH may be predictive of symptomatic vasospasm.

Keywords: Intracranial aneurysm; platelet derived growth factor; subarachnoid haemorrhage; vasospasm.

Introduction

After rupture of an intracranial aneurysm there is a significant activation of the haemostatic system [5, 11]: increased aggregability of platelets (PLT) after endothelial injury, the activation of the thrombin/antithrombin (TAT) system and the release of vasoconstrictor compounds such as serotonin and thromboxane B2 (TxB2) have been demonstrated in previous studies [3, 17, 19, 22, 23]. PLT function and aggregability are enhanced in the early stage of SAH [17] and if the enhanced PLT function continues after day 5 following SAH, the risk for symptomatic vasospasm is higher. Juvela *et al.* [11] found in peripheral blood samples that even if platelet activation is significantly increased in the first two weeks after SAH, symptomatic vasospasm occurs only in a proportion of patients with highest thromboxane B2 release.

High serum levels of TAT complex were related to neurological grading on admission, CT findings and the outcome of patients [5], and also in CSF of patients presenting vasospasm, levels of TAT complex were higher than those of patients with an uncomplicated course [24]. TAT facilitates the gene expression of endothelin 1 [26], the liberation of serotonin and of platelet derived growth factor (PDGF) from platelets: all these events have been related to the pathogenesis of vasospasm [7].

A lot of vasoactive compounds have been found in CSF after aneurysm rupture and are supposed to be involved in the pathogenesis of cerebral vasospasm [7, 27]: PDGF is released from activated platelets and is considered one of the most potent vasoconstrictor agents [1], but few studies have addressed the question whether PDGF might play a significant role in the pathophysiology of SAH. In the present study we have measured cisternal CSF levels of PDGF in a

large series of patients admitted for SAH and addressed the question whether these might be related to the clinical aspects of SAH with special regard for symptomatic vasospasm.

Methods and Patients

Clinical Material

In the present study a series of 72 patients (29 males and 43 females) operated on for intracranial aneurysms was evaluated. In 18 cases an unruptured intracranial aneurysm was diagnosed during angiographic studies performed for other reasons (previous episodes of transient cerebral ischaemia): these cases represent the control group.

Fifty-four patients admitted with diagnosis of aneurysmal SAH within the first 72 hours after the haemorrhage were included and classified according to different parameters: timing of surgery, CT classification at diagnosis according to Fisher *et al.* [4] and World Federation of Neurosurgical Societies (WFNS) grading. The procedures followed were in accordance with institutional guidelines. The study protocol was approved by an Institutional Review Committee and every patient (or relatives) was informed before surgery of cisternal CSF sampling and gave informed consent.

CSF samples were obtained at surgery by cisternal puncture of the subarachnoid cistern nearest to the aneurysm before aneurysm isolation and exclusion. Patiens were divided into the following groups: (a) unruptured aneurysms (controls); (b) patients operated on within 72 hours after SAH; (c) patients undergoing delayed surgery because of clinical and technical considerations (general condition, availability of intensive care unit, angiographic patterns). Vasospasm was assessed by angiography and trans-cranial doppler (TCD) monitoring. Patients operated on day 1–3 had angiography on admission, prior to surgery, while patients operated after day 10 from last SAH never had angiography before day 8 after the haemorrhage; moreover, all patients were studied with serial TCD measurements every second day after SAH, in order to identify the occurrence of vasospasm during the maximal risk time.

The modifications of CSF levels of PDGF caused by the haemorrhage were studied considering also the subgroup of patients operated on within 72 hours after SAH, in order to avoid discrepancies due to differing timing of CSF sampling. In the same group we analysed the relationship between PDGF levels in CSF and the amount of subarachnoid blood clots as classified by CT scan, comparing patients presenting pure subarachnoid blood and patients presenting with haematoma and intraventricular bleeding. Routine coagulative parameters (platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen) were measured on peripheral blood samples on admission in order to exclude the presence of coagulative disorders and to verify the presence of any correlation between modifications of such parameters and clinical patterns.

Symptomatic vasospasm was diagnosed when an overt neurological deterioration was accompanied by TCD velocities over 160 cm/sec and severe arterial narrowing on angiography.

Analytical Methods

Cerebrospinal Fluid Handling

CSF samples obtained at surgery were immediately centrifuged at 6500 rpm (Microcentrifuge, Microcentaur, MSE). The supernatants were used as specimen for the measurement of PDGF activity. An aliquot of supernatants was used in order to measure eventual red and white cells residual. The specimen were frozen in liquid nitrogen and stored at –80° C until analysis.

Measurement of PDGF

Cisternal CSF levels of PDGF were measured using a commercially available reagents (Amersham, Italia, Milan, Italy). This assay measures specifically the B chain of PDGF. Values are expressed as pg/ml of CSF. The assay sensitivity is 24 pg/ml.

Statistical Analysis

Statistical evaluation for intergroup comparison was performed using one-way analysis of variance (ANOVA) and Student's t-Test for unpaired data; linear regression analysis was performed in order to verify any significant correlation between PDGF levels in CSF and the day of surgery or the age of patients. Statistical procedures were performed according to Estatix statistical package for Macintosh; statistical significance was accepted for $P<.05$.

Results

Routinely used coagulative parameters are not significantly related to CT characteristics, WFNS grading on admission and occurrence of vasospasm.

Eighteen cases without radiological and clinical signs of SAH were considered as control patients and classified as WFNS=0, CT=0: mean cisternal CSF level of PDGF was 885.0±104.5 pg/ml; 36 cases were in good clinical condition (classified in WFNS grade 1 and 2) on admission; 18 patients were classified in WFNS grade 3 and 4; Table 1 shows that cisternal CSF level of PDGF was significantly lower in patients in good clinical condition (WFNS 1 and 2) than in patients admitted in poor neurological condition (WFNS grade 3 and 4); 20 patients were operated on between day 1 and 3 from the last SAH episode: mean cisternal CSF level of PDGF was 1917.5±459.4 pg/ml. In 34 patients treated according to the delayed surgery protocol, mean cisternal CSF level of PDGF was 995.3±73.8 pg/ml. Statistical analysis (ANOVA) showed significant differences between groups ($F=4.81$; $P=0.011$).

Table 1. *Cisternal CSF Levels of PDGF in Patients with Intracranial Aneurysms Classified According to WFNS on Admission*

	n	PDGF (pg/ml)
WFNS 1	20	852.5 ± 118.2
WFNS 2	16	1161.9 ± 147.6
WFNS 3 and 4	18	2094.1 ± 512.4[a]

Statistical analysis: ANOVA shows significant difference between groups ($F=4.55$; p 0.015). Student's t test: [a] $p<0.02$ WFNS 1 vs. WFNS 3/4.

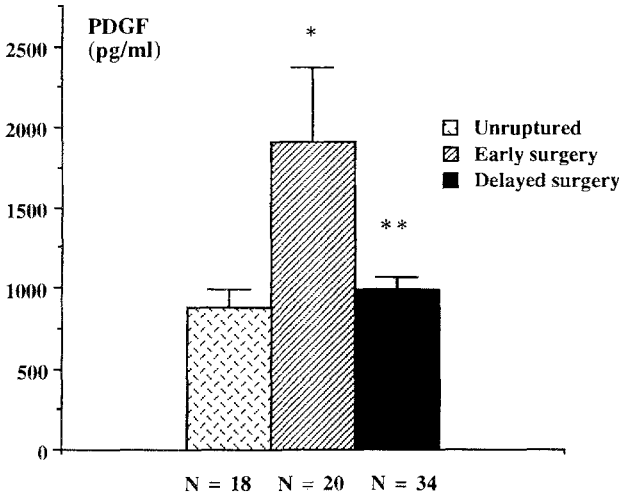

Fig. 1. Bar graph representation of PDGF cisternal CSF levels in 72 patients operated on for intracranial aneurysms. Statistical analysis: ANOVA shows statistical difference between groups (F=4.81; p 0.011); Student's t test: *p<0.05 unruptured vs. early surgery; **p<0.02 early vs. delayed surgery

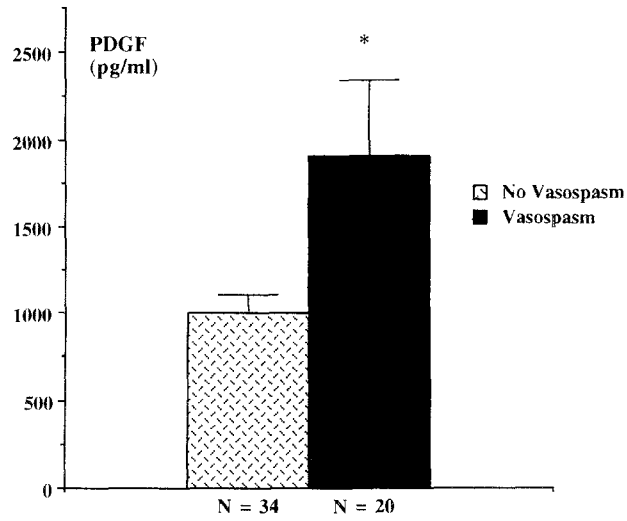

Fig. 2. Bar graph representation of PDGF cisternal CSF levels in patients with vasospasm and without symptomatic vasospasm. Statistical analysis: Student's t test: *p<0.02

In particular, mean cisternal PDGF level in CSF in unruptured aneurysms was significantly lower (p<0.05) than in patients operated on day 1–3 after SAH (Fig. 1) but was not significantly different from that of patients operated in a delayed phase. Moreover, mean cisternal CSF level of PDGF in patients operated on within day 3 after SAH was significantly higher (P<0.02) than in patients operated on in the delayed phase.

ANOVA showed that there was no significant difference (F=1.94; P=0.13) between cisternal CSF levels of PDGF when considering subgroups of patients classified according to the amount of subarachnoid blood on CT scans (Table 2).

In particular considering the subgroup of patients operated on within 72 hours after SAH, we found no significant difference between cisternal CSF level of PDGF in patients with thin subarachnoid blood clots when compared to those of patients with consistent blood clots (ANOVA: F=1.90; P=0.18).

Among the 54 patients operated on after SAH, 20 presented ischaemic complications due to vasospasm: in these cases mean cisternal PDGF level (1919.0±442.2 pg/ml) was significantly higher (P<0.02) than in the 34 patients without symptomatic vasospasm (Fig. 2). Considering the different timing of surgery, in the subgroup of patients operated on within day 3 after SAH, 6 presented vasospasm and

Table 2. *Cisternal CSF Levels of PDGF in Patients with Intracranial Aneurysms Classified According to CT Scan Deposition of Blood (Classification by Fisher et al., see Ref.)*

	n	PDGF (pg/ml)
CT grade 1	17	1102.4 ± 229.3
CT grade 2	15	1040.0 ± 183.2
CT grade 3 and 4	22	1720.5 ± 389.8

Statistical analysis: ANOVA shows no significant difference among groups (F=1.50; p 0.23).

Table 3. *Cisternal CSF Levels of PDGF in Patients with Intracranial Aneurysms Classified According to the Occurence of Symptomatic Vasospasm and Timing of Surgery*

	n	PDGF (pg/ml)
Acute surgery		
Vasospasm	6	3941.7 ± 1121.9[a]
No vasospasm	14	1050.0 ± 200.7
Delayed surgery		
Vasospasm	14	1039.3 ± 80.2
No vasospasm	20	964.5 ± 113.4

Student's t test: [a]p<0.02.

had mean cisternal CSF PDGF level (3941.7±1121.9 pg/ml) which was significantly higher ($P<0.01$) than in 14 patients without vasospasm (1050.0±200.7 pg/ml).

In patients operated on day 10 after SAH, 14 presented symptomatic vasospasm before surgery: mean cisternal CSF level of PDGF was 1039.3±80.2 pg/ml while in 20 cases considered as vasospasm free, the mean cisternal CSF level of PDGF was 964.5±113.4: the difference was not statistically significant (Table 3).

The linear regression analysis showed that cisternal CSF levels of PDGF were significantly correlated neither to the age of patients ($R=0.04$, $P=0.742$) nor to the day of surgery ($R=0.13$; $P=0.263$) nor to routine haemostatic parameters.

Discussion

The pathogenesis of symptomatic vasospasm and delayed cerebral ischaemia following SAH is still unknown and may be ascribed to many factors [13].

Therefore changes in the haemostatic system and in particular patterns of platetet activation after the haemorrhage have been related to the development of ischaemic complications [5, 11, 17]. In a previous study [19] we found that after SAH, TxB2 was the most represented arachidonate metabolite in cisternal CSF, but the higher levels of TxB2 were not significantly related to the occurrence of vasospasm and may be considered only as the expression of PLT activation in subarachnoid spaces after the aneurysm rupture.

Other authors suggested that after SAH, even in the presence of a significant PLT activation, the occurrence of symptomatic vasospasm might depend on some mechanisms which are qualitatively enough to stimulate platelet function and favour the release of compounds which may act as spasmogens [11].

In the present study we found (a) a marked increase of PDGF levels in the subarachnoid spaces in the early phase (within 72 hours) after SAH and (b) that higher levels of PDGF found in cisternal CSF of patients operated on within 72 hours are predictive of the occurrence of symptomatic vasospasm.

The major source for PDGF are platelets alpha granules activated during coagulation. PDGF was identified as a powerful mitogenic growth factor for fibroblasts, smooth muscle cells and glial cells [14, 28, 29]. Beck *et al.* [1] have shown that PDGF is one of the most potent vasoconstrictor compounds and when it interacts with responsive cells, it induces the turn over of phosphatidylinositol, the release of arachidonic acid and the formation of eicosanoids [8, 20]: all these biological effects have been demonstrated as important pathophysiological features of subarachnoid haemorrhage (SAH) and vasospasm [6, 18, 21]. While some authors have reported elevated levels of PDGF in plasma of patients bearing intracranial neoplasms [15], and elevated concentrations of PDGF in cystic fluid of malignant neuro-epithelial tumours [16], scarce data ara available on levels of PDGF in CSF in physiological or pathological conditions. A "normal" CSF value is not available in the current literature. Also in the series by Honma *et al.* [9] in 6 patients with non-cerebrovascular lesion the CSF PDGF level was below the detection limit (100 pg/ml).

On the other hand, few data are consistent with the possibility that SAH may induce a significant release of PDGF in subarachnoid spaces and if elevated cisternal levels of PDGF may be correlated with the incidence of vasospasm and ischaemic complications. Significant arterial narrowing and thickening of the wall in the lamina elastica were observed in cats after PDGF injection into cisterna magna [10]. In experimental conditions [12] the development of proliferative angiopathy following SAH induction is inhibited by heparin which is considered an inhibitor of PDGF.

Finally, Honma *et al.* [9] found elevated concentrations (>100 pg/ml) within 3 days after SAH, but the low number of patients did not allow any correlation with the clinical course, vasospasm occurrence and outcome.

In the present study we found that the significant increase of PDGF levels in CSF occurs only in the early stage and that CSF levels of PDGF are not correlated with the amount of subarachnoid blood (Table 2): this would confim that platelet activation and the release of spasmogens depend on the haemorrhage "per se" and not on the amount of subarachnoid blood and that only in a proportion of patients might this result in a higher release of PDGF. Moreover, we found that in patients operated on in the acute phase there is a significant relationship between elevated levels of PDGF and the occurrence of symptomatic vasospasm (Fig. 1).

Yamamoto *et al.* [25] hypothesised that an active interaction between proliferative myofibroblasts and the extra-cellular matrix might re-arrange the ultrastructure of vascular connective tissue holding the artery in the characteristic spastic state of so-called

proliferative angiopathy. PDGF may be released from platelets in subarachnoid spaces early after aneurysm rupture and may exert its effects from the cisternal site giving an intracellular signal starting the expression of mRNA which leads to proliferative changes in the arterial wall; moreover, PDGF may act from the intimal site [12] after platelets have accumulated on the intimal surface as a physiological response to endothelial injury.

However, some questions still remain unanswered: the first problem is that no early CSF level of PDGF was obtained in patients who underwent delayed surgery; levels of PDGF found in patients with symptomatic vasospasm and operated on in the delayed phase are not significantly differently elevated and this might be simply reflective of the natural course of PDGF elevation in CSF after SAH, and not reflective of any other factor.

Another question concerns the level of PDGF in cisternal CSF of patients with unruptured aneurysms: the presence of detectable levels of PDGF may be explained by a local base-line activation of PLT related to the endothelial structural alteration present in the aneurysm wall. When the aneurysm rupture occurs there is a marked increase of PDGF levels which "represent" a sustained PLT activation: in this sense greater release of PDGF occurs, a higher risk of vasospasm exists, as suggested by the highest cisternal CSF levels of PDGF found in patients presenting symptoms due to ischaemic complications.

In conclusion, even if it still remains questionable whether PDGF may be considered among the myriad of proposed spasmogens, the elevation of cisternal CSF levels early after SAH might have a predictive value regarding the occurrence of symptomatic vasospasm.

Acknowledgements

Authors are indebted to M. Brunelli, mecenate of neurosurgical research; this study was supported by grant of the IRCCS Policlinico S. Matteo, 1995.

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Comments

The article of Gaetani *et al.* with the title "Platelet derived growth factor and subarachnoid haemorrhage: a study on cisternal cerebrospinal fluid" is well written and contains interesting data. The authors removed CSF from the cistern surrounding an aneurysm during the operation and looked for the platelet derived growth factor content.

Surprisingly enough in asymptomatic cases the level of PDGF was as high as the level of PDGF in patients operated on more than 10 days after a subarachnoid haemorrhage. In the patients operated on within 72 hours after the subarachnoid haemorrhage a much higher level of PDGF was found and the level in patients with vasospasm [6] was significantly higher than the level in patients without vasospasm. This is the most remarkable and the most important finding in this study.

C. Tulleken

The authors report cisternal cerebrospinal fluid levels of PDGF measured in a series of 72 patients operated upon for intracranial aneurysms. They hypothesize that PDGF, a potent vasoconstrictor agent released from activated platelets, may be related to vasospasm. Based on their results the authors conclude that there is a significant release of PDGF early after SAH and that early cisternal PDGF levels may be predictive of symptomatic vasospasm.

Thanks to a sound methodology and a clear description of the results the authors present new clinical data on PDGF in SAH. These results are of interest for the scientific community and will help develop new investigations of PDGF as a spasmogen.

The pathophysiology of SAH and vasospasm is particularly complex, resulting in the activation of numerous biochemical cascades. It is, therefore implssible to elaborate one unifying theory. The different possible mechanisms need to be investigated separately and this report certainly adds information to the PDGF file.

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