C-reactive protein and vasospasm after aneurysmal subarachnoid hemorrhage[1]

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ABSTRACT

PURPOSE: To evaluate the relationship between C reactive protein levels and clinical and radiological parameters with delayed ischemic neurological deficits and outcome after aneurysmal subarachnoid hemorrhage.

METHODS: One hundred adult patients with aneurismal SAH were prospectively evaluated. Besides the baseline characteristics, daily C-reactive protein levels were prospectively measured until day 10 after subarachnoid hemorrhage. The primary end point was outcome assessed by Glasgow Outcome Scale, the secondary was the occurrence of delayed ischemic neurological deficits (DINDs).

RESULTS: A progressive increase in the CRP levels from the admission to 3rd postictal day was observed, followed by a slow decrease until the 9th day. Hemodynamic changes in TCD were associated with higher serum CRP levels. Patients with lower GCS scores presented with increased CRP levels. Patients with higher Hunt and Hess grades on admission developed significantly higher CRP serum levels. Patients with higher admission Fisher grades showed increased levels of CRP. A statistically significant inverse correlation was established in our series between CRP serum levels and GOS on discharge and CRP levels.

CONCLUSIONS: Higher C-reactive protein serum levels are associated with worse clinical outcome and the occurrence of delayed ischemic neurological deficits. Because C-reactive protein levels were significantly elevated in the early phase, they might be a useful parameter to monitor.

Key words: C-Reactive Protein. Vasospasm, Intracranial. Subarachnoid Hemorrhage.

Introduction

Cerebral vasospasm is a prolonged, sometimes severe narrowing of cerebral arteries following a subarachnoid hemorrhage (SAH), consisting the major cause of morbidity in this disease[1-4]. Angiographic vasospasm is common after rupture of an aneurysm, with overall incidence of 50% to 90%, but only 20% to 30% of patients develop clinical vasospasm, as a result of ischemia and delayed ischemic neurological deficits[5-9].

Pathogenesis of vasospasm is due to smooth muscle contraction (entry and release of calcium and activation of calcium / calmodulin-dependent myosin light-chain kinase), endothelial injury (nitric oxide and endothelin-1 derangement), inflammation (inflammatory cytokines, intercellular adhesion molecules and genetic upregulation of inflammatory, proliferative and extracellular matrix-regulating genes) and vessel remodeling[1,3,10-13].

With a modern SAH management, the risk for death and permanent disability from vasospasm decrease for less than 10%, but it is still remains one of the leading causes of preventable poor outcome after rupture of an aneurysm[14-16]. So, predict vasospasm can determinate the outcome and decrease the morbidity rates in this condition. Risk factors have been identified, including poor neurological grade or loss of consciousness on admission (Hunt-Hess scale), clot subarachnoid volume (Fisher grade scale), cigarette smoking, preexisting hypertension, gender, patient age, aneurysm location, and inflammatory markers (interleukine-6, c reactive protein and leucocytes count)[17-22].

The aim of this study was to assess the correlation of risk factors, including inflammatory parameters (CRP levels) with vasospasm and outcome in patients with SAH.

Methods

This prospective observational study was carried out in tertiary care center during a 4-year period (2009-2013). Approved by the Research Ethics Committee of São Paulo State University(UNESP).

One hundred adult patients with confirmed aneurysmal SAH were included in this prospective observational study. Fifth-six man (56%) and fourth-four women (44%), with mean age of 48.03 years (range 18-65) were presented with 126 intracranial aneurysms. The inclusion criteria were the diagnosis of aSAH and cerebral aneurysms established by a CT scan and four-vessel DS angiography study, patient age >18 years, patient admission to our institutions within the first 24 hours postictus. The exclusion criteria were concomitant or recent acute myocardial infarction, recent surgery (≤30 days) prior to the event, and/or clinical or laboratory evidence of chronic systemic infection or acute infection. In addition, patients who died before completing 10 days of treatment were not included.

Patient demographics, clinical status on admission (Glasgow Coma Scale (GCS) and Hunt and Hess grades), head CT scans, severity of the SAH blood clot load (Fisher grades), location of a ruptured aneurysm (standard four-vessel DS angiography) and neurological examinations on admission and daily thereafter were recorded. Surgical clipping was performed in 57 (57%) of the 100 patients for 72 (57.14%) of the 126 aneurysms, whereas endovascular treatment was used in 43 patients (43%) for 54 (42.86%) of the 126 aneurysms.

The clinical severity at time of admission was assessed according to Hunt-Hess grade and dichotomized into two groups (HH 1-3 and 4-5). The radiological severity was assessed according to the Fisher grade; grades 1 and 2 were combined into 1 group. The selection of surgical versus endovascular treatment was based on criteria, such as the anatomical location of the lesion, the size and morphological features of the aneurysm, the presence of multiple aneurysms, the presence of a mass effect caused by the aneurysm and/or an associated hematoma, and the patient's neurological and general medical condition and preference.

The primary end point was the dichotomized clinical outcome 3 months after SAH, defined as favorable (Glasgow Outcome Scale [GOS] score of 4-5) and unfavorable (GOS score of 1-3). Outcome was assessed in the outpatient clinic by a neurologist who was blinded to the inflammatory parameter. The occurrence of DIND was the secondary end point, defined by neurological findings with narrowing in DS angiographic study.

The serum CRP levels were measured daily between admission and the tenth day, and the measurements obtained were recorded. Transcranial Doppler (TD) was performed daily. It was approved for both local ethics committee.

Categorical variables were described using frequency and percentage. Because the continuous variables were not normally distributed, except for age, values were described as median and quartiles if not otherwise indicated. Categorical variables were compared between the groups by use of x^2 test or the Fisher exact test. Serum CRP levels were logarithmically transformed for statistical analysis. Independent t test or Mann-Whitney U test was applied as appropriate. In patients with DINDs, further analysis within the group was performed, stratifying the timing by the occurrence of DINDs. Each measured inflammatory biomarker was analyzed by repeated-measures analysis of variance or the Friedmann test followed by post hoc multiple comparisons

with Bonferroni correction. A value of $p < 0.05$ was regarded as statistically significant. To examine the association between the longitudinal values of each inflammatory parameter and the primary outcome, unconditional logistic regression, unadjusted and adjusted for the confounding covariates, was performed.

In addition, with regard to the occurrence of DINDs, the unadjusted and adjusted predictive values of inflammatory parameters in the early phase (days 3-7) were evaluated by unconditional regression. A conditional logistic regression with stepwise forward selection was performed to study the association of various relevant risk factors, including significant inflammatory parameters, with unfavorable outcome. The significance level for a new factor to enter the model was $p = 0.05$. The significance level specified for a covariate to be removed was $p = 0.10$. For the significant factors, odds ratios and their 95% confidence intervals were calculated. Receiver-operating characteristic curves for the prediction of neurological outcome were generated for the significant predictors. IBM SPSS Statistics 20.0 software was used.

Results

The admission GCS scores ranged from 3 to 15 (mean=14). Hunt and Hess scores on admission ranged from I to V (mean=2.5), and Fisher grades from 1 to 4 (mean=1.5). The GOS scores on discharge ranged from 2 to 5 (mean=4.2).

A progressive increase in CRP levels from admission to the third day post ictus was observed, followed by a slow decrease until the ninth day (Figure 1).

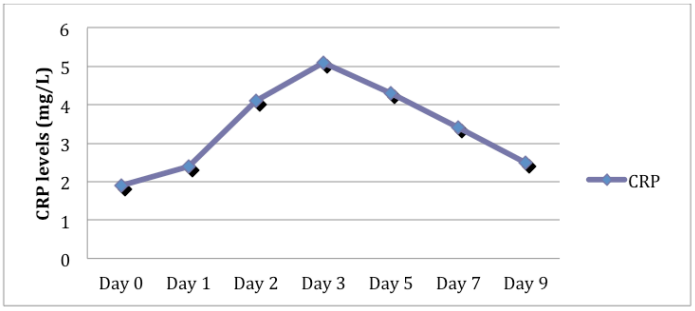

FIGURE 1 - Schematic representation of summated measured CRP serum levels of our patients.

Patients with lower GCS scores presented increased CRP measurements (correlation coefficient methodology; $z = -8.912$, $p<0.0001$, $r = -0.89$). Patients with higher Hunt and Hess grades on admission developed significantly higher serum CRP levels (correlation coefficient methodology; $z = 6.941$, $p < 0.0001$, $r = 0.81$) (Figure 2).

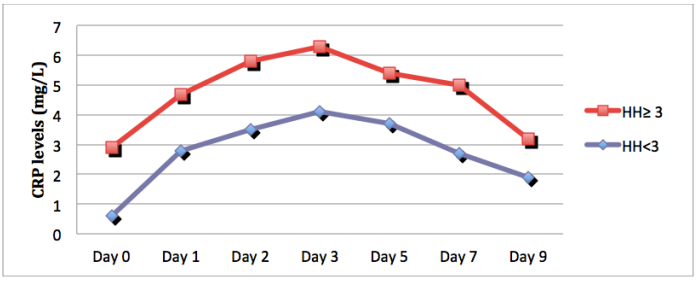

FIGURE 2 - Schematic representation of serum CRP levels with regard to the admission Hunt Hess score (HH).

Similarly, patients with higher Fisher grades on admission showed increased levels of CRP (correlation coefficient methodology; $z = 7.821$, $p < 0.0001$, $r = 0.86$) (Figure 3).

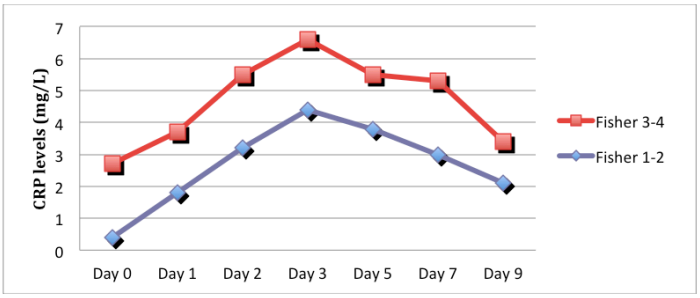

FIGURE 3 - Schematic representation of serum CRP levels in patients with admission Fisher score 1-2 versus patients with Fisher score 3-4.

Occurrences of clinical vasospasm were significantly correlated with higher CRP levels (correlation coefficient methodology; $z = 7.921$, $p < 0.0001$, $r = 0.75$) and patients with hemodynamic changes in transcranial Doppler showed higher CRP levels than patients without vasospasm (correlation coefficient methodology; $z = 8.421$, $p < 0.0001$, $r = 0.88$) (Figure 4).

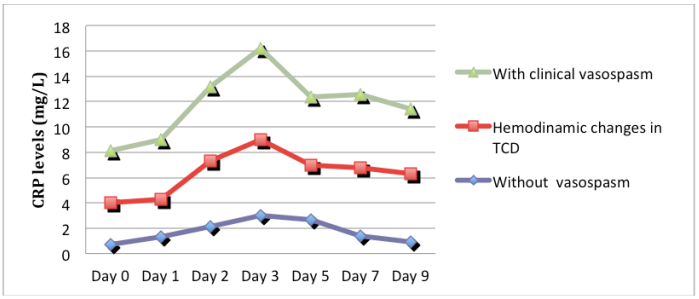

FIGURE 4 - Schematic representation of serum CRP levels in patients with and without vasospasm and with hemodynamic changes in TCD.

There was no statistically significant difference in serum CRP levels between the group of patients undergoing surgical clipping and those undergoing endovascular coil occlusion. With regard to their GOS scores, patients with higher serum CRP levels (correlation coefficient methodology; $z = -6.181$, $p<0.0001$,

r = −0.81) (Figure 5) presented less favorable outcomes. A statistically significant inverse correlation was established in our series between serum CRP levels and GOS scores.

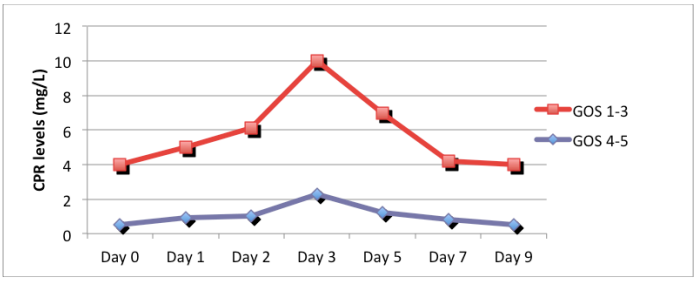

FIGURE 5 - Schematic representation of serum CRP measurements in patients with GOS score 4-5 versus patients with GOS score 1-3 at discharge.

Logistic regression analysis data are showed in Table 1. After adjustment, remain associated with DIND and poor outcome: a) GCS on admission, that showed the lower initial GCS, the higher chance of DIND (OR=2.0, 95% IC 1.1 a 3.4); b) Hunt-Hess grade on admission ≥ 3 has 3.7 more chance to develop ischemia and poor outcome than HH < 3 (OR = 3.7, 95% IC 1.8 a 4.5); c) initial Fisher grade, that showed the higher initial score the higher chance to develop DIND (OR = 1.9, 95% IC 1.3 a 2.8); d) number of intracranial aneurisms, the higher the number of lesions the higher chance to develop DIDN (OR = 0.9, 95% IC 0.8 a 0.9); e) CRP levels, the higher serum CRP levels, the higher chance to develop DIDN (OR = 1.8, 95% IC 1.4 a 2.1); f) hemodynamic changes in Transcranial Doppler, showed speed higher than 120 cm/s have more chance to develop DIDN (OR = 3.4, 95% IC 1.6 a 6.8).

TABLE 1 - Logistic regression analysis data results.

Variable	Stimatives			CI (95%) OR		
	Coeficient	Wald	p	OR	IL	SL
Constant	-1.1	7.1	0.0076			
GCS (admission)	0.7	5.8	0.0161	2.0	1.1	3.4
HH (admission)	1.3	12.9	0.0003	3.7	1.8	7.5
EF(admission)	0.6	9.6	0.0019	1.9	1.3	2.8
Number of aneurisms	-0.1	19.6	0.0000	0.9	0.8	0.9
CRP (serum)	0.7	6.2	0.0021	1.8	1.4	2.1
TCD > 120 cm/s	1.1	7.3	0.0067	3.4	1.6	6.8

OR: odds ratio; IL: inferior limit; SL: superior limit.

Discussion

Cerebral vasospasm after SAH is common, potentially devastating, and incompletely understood. Delayed cerebral vasospasm is associated with high rates of morbidity and mortality. Several inflammatory mechanisms are directly involved in the pathogenesis of cerebral vasospasm, with increased levels of various soluble adhesion molecules (such as E-selectin, intercellular adhesion molecule-1 and vascular adhesion molecule-1) and cytokines (such as IL-6 and IL-1) that have been detected in the plasma and CSF of patients with aSAH. Inflammation accompanying SAH may be a critical pathway underlying the development of cerebral vasospasm. Inflammation is a complex and multifaceted response aimed to ultimately defend against foreign antigens[8,9,16-20]. In the instance of SAH, a complex series of cellular and molecular events is elicited by the presence of blood clot in the subarachnoid space, culminating in a robust inflammatory response. Although the possible role of inflammation in the genesis of cerebral vasospasm has been recognized for some time, its cellular and molecular basis and putative importance have not been more clearly defined until recently[2,3,21,22].

Experimental and clinical evidence suggests that Intercellular Adhesion Molecule 1 (ICAM-1) mediated leukocyte migration may play a crucial role in the pathogenesis of cerebral vasospasm[9-13]. SAH increases endothelial ICAM-1 expression[1,3,4,5,9,14,15] and resultant perivascular leukocyte migration[1,3,4,5,9,16,17]. Furthermore, serum ICAM-1 level correlates with the onset of cerebral vasospasm[1,3,6-9]. Perivascular chemokine-activated inflammatory cells synthesize and release endothelin-1, a potent vasoconstrictor, as well as superoxide free radicals, leading to inactivation of nitric oxide (NO) and vasoconstriction[1,3,6-14,15]. Anti-ICAM-1 antibodies decrease leukocyte migration and attenuate cerebral vasospasm after SAH[1,3,6-9].

CRP is a sensitive inflammatory marker, with synthesis in hepatocytes is strongly stimulated by interleukin-6[1,2,3,6,7,22,23]. Additionally, IL-1, which has been implicated in the pathogenesis of cerebral vasospasm, also represents a strong stimulus for CRP synthesis[1-5]. So, elevated concentrations of CRP may well be associated with an increased possibility of developing cerebral vasospasm and subsequently a DIND[1,3,24-29].

There was a strong inverse correlation between admitting GCS scores and CRP level in serum (r = −0.89 and r = −0.82, respectively). Hunt and Hess and Fisher grades were also correlated in a statistically significant fashion with the CRP measurements in our cohort. These data clearly indicates that CRP levels significantly relate with the severity of aSAH and occurrence of

vasospasm. Furthermore, the elevated CRP levels were associated with worse clinical outcome, as expressed in GOS. Our strict inclusion criteria minimized the influence of other confounding factors such as systemic infection or concomitant systemic conditions, and statistical analysis is compelling to define the influence of CRP levels on vasospasm occurrence and neurological final outcomes. Unfortunately, the clinical significance of elevated serum CRP measurements in patients sustaining aSAH is confounded by the fact that most of these patients may have other concomitant systemic infections or pathological conditions that could potentially result in increased CRP serum concentrations. Additionally, the surgical manipulation in these patients could influence the systemic CRP levels.

It is well known that clinical outcome in patients with aSAH is multifactorial. The association between CRP levels systemically with the clinical outcome may well be influenced by other parameters in a complex and frequently unpredictable way. In addition, CRP represents a sensitive but nonspecific inflammatory marker[1-4]. A large-scale, multicenter, prospective clinical study is necessary to validate our results and to determine the role of serum CRP in the identification of patients at high risk for developing cerebral vasospasm[1,2,7-9].

Also, we found that clinical and radiological parameters can help the assistant to detect patients with more chance to develop vasospasm. The unconditional logistic regression analysis associated GCS on admission, Hunt-Hess grade on admission, initial Fisher grade, the number of intracranial aneurisms and hemodynamic changes in Transcranial Doppler with predictive finding after a SAH.

Conclusion

Higher C-reactive protein serum levels are associated with worse clinical outcome and the occurrence of delayed ischemic neurological deficits. Because C-reactive protein levels were significantly elevated in the early phase, they might be a useful parameter to monitor.

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