

Pre- and post-operative values of serum CRP in patients undergoing surgery for brain tumour

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Abstract

Objective: To determine the concentration of C-reactive protein in pre- and post-operative serum samples of brain tumour patients in order to detect the potential risks of post-operative infections.

Methods: Serum C-reactive protein was measured on pre- and post-operative Day 1, Day 2 and Day 7 in 18 patients who underwent surgery for brain tumours. The study was performed at the Neurosurgical Ward, Jinnah Postgraduate Medical Centre, Karachi, from May 2007 to April 2008. Mean pre-operative patients and control values were compared using Mann-Whitney or Wilcoxon tests for comparing between pre- and post-operative values. P-value was considered significant at <0.05 .

Results: Five (27.7%) of the 18 pre-operative patients had elevated serum concentrations i.e. $>5.0\text{mg/L}$ but no statistically significant difference was found when compared with healthy controls, with mean 4.4 ± 6.6 and 0.9 ± 0.7 , respectively. Significantly raised serum concentrations were observed in all post-operative samples when compared with pre-operative samples. Serum CRP concentrations significantly increased post-operatively on Day 1, with mean value of $102.9\pm 82.0\text{mg/L}$ ($p<0.0005$), and further increased on Day 2 with mean value of $166.9\pm 128.1\text{mg/L}$ ($p<0.0005$), but declined on Day 7, with mean value of $42.7\pm 63.6\text{mg/L}$ ($p<0.005$).

Conclusion: Pre-operative serum C-reactive protein concentrations of 28% of the patients were elevated, suggesting an association with brain tumours. Post-operative serum concentrations were significantly higher than those noted before the surgery. Absence of a fall of concentration from peak value on post-operative Day 2 or a secondary rise from post-operative Day 7 could be alarming for inter-current infection.

Keywords: C-reactive protein, Brain tumour, Pre- and Post-operative infections. (JPMA 64: 271; 2014)

Introduction

C-reactive protein (CRP), one of the acute-phase proteins, is considered to be a sensitive systemic marker of inflammation following tissue damage.¹ CRP synthesis in liver (hepatocytes) and its rate of expression primarily increases in response to injury or infection. Expression is induced predominantly by interleukin (IL-6), and also by IL-1 and tumour necrosis factor α (TNF- α).^{2,3} In healthy subjects, CRP concentration is very low in the blood, with a reference range between 0-5mg/L. The concentrations of CRP dramatically rise during inflammatory processes occurring in the body. A raised CRP concentration is unequivocal evidence of an inflammatory response; however, viral infections do not usually cause a raised CRP and neither do some autoimmune diseases i.e. systemic lupus erythematosus (SLE).⁴ Following an acute-phase stimulus, the concentration may rise by about 6 hours,

with a peak value around 48 hours, and may further increase depending on the severity of infection.²

In most diseases, the CRP value indicate ongoing inflammation more accurately than do other laboratory parameters of inflammation response such as plasma viscosity, erythrocyte sedimentation rate (ESR) and leucocyte count (LC).^{2,3} In recent years the role of CRP in relation to cancer has been extensively investigated. It is widely accepted that chronic inflammation increases the risk of cancer. For instance, inflammatory bowel diseases, human immune-deficiency virus (HIV), viral hepatitis B, human papilloma virus and rheumatoid arthritis are all associated with an increased risk of specific types of cancers.⁵ Given that cancer is related to several forms of inflammation, plasma CRP concentrations have also been measured in cancer patients. High serum concentration has been demonstrated in malignant melanoma, choroid meningioma, lymphoma, gastric adenoma and mucosal carcinoma, colorectal, lung, ovarian and renal cancers.^{3,6-12}

Furthermore, it has also been shown that increased plasma CRP concentrations are independently associated with an increased risk of colorectal cancer, suggesting an association between chronic inflammation and colorectal

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cancer.¹³ Most recent studies show that increased CRP level was an independent factor contributing to the likelihood of a poor outcome in lung and thoracic esophageal squamous cell cancers.^{14,15}

This study focussed on the clinical utility of CRP with the aim of checking its sensitivity for predicting post-operative infection in neurosurgical patients as an increased level of this inflammatory marker is considered an indicator of infection.

Patients and Methods

The measurement of pre- and post-operative serum concentration was performed on patient samples as described in our previous study.¹⁶ The study was carried out at the Neurosurgical Ward, Jinnah Postgraduate Medical Centre, Karachi, from May 2007 to April 2008. The study design was approved by the Institutional Ethical Review Board (IERB) of Jinnah University for Women (JUW), Karachi. The patients underwent initial computed tomography (CT) and magnetic resonance imaging (MRI) and were diagnosed with different types of brain tumours.

All participants were fully informed about the study and consent for participation was obtained from each of them.

The CRP concentration was measured turbidimetrically on an Advia 2400 analyser, using their CRP kit (Cat. No. 039-21431, Hampshire, UK). Experimental data were statistically analysed with SPSS 20. Since the overall trend of median and mean concentration of CRP was almost similar in normal healthy controls, therefore mean value was used to present the data. All data was compared by Mann-Whitney (Unpaired) or Wilcoxon (Paired) non-parametric tests. The p-value was considered significant at <0.05.

Results

The patient group comprised 9 (50%) females and 9 (50%) males, with an overall mean age of 30.3 ± 13.5 years (range: 7-65 years). Normal healthy subjects comprising 9 (50%) males and 9 (50%) females with a mean age 33.1 ± 10.3 years (range: 19-55) represented the control group. On CT and MRI, pathologies found included 5 (27.7%) gliomas, 5 (27.7%) meningiomas, 2 (11.11%) pituitary tumours, ependymoma, arteriovenous malformation (AVM), lymphoma, medulloblastoma, acoustic neuroma and orbital neuroblastoma each.

There were no major complications during surgery in any of the patients. Almost no pre-operative patients had fever, while some post-operative patients had mild fever. No pre- or post-operative infection was recorded during

the study period. Serum concentrations of CRP in normal healthy subjects and pre-operative patients were within the reference range i.e. <5.0 mg/L, with mean values of 0.9 ± 0.7 and 4.4 ± 6.6 , respectively. Among the pre-operative patients, 13 (72%) had normal CRP concentrations in serum (<5.0), while 5 (27.7%) patients had elevated concentrations (>5.0 mg/L). There was no statistically significant difference between the CRP concentrations in serum of healthy controls and patients (pre-operative) with brain tumours ($p=0.245$).

In post-operative patients, CRP concentrations were significantly increased relative to the pre-operative period. CRP concentrations in serum were elevated on post-operative Day 1 with a mean value of 102.9 ± 82.0 mg/L and further increased (i.e. 62.2%) on Day 2 with a mean value of 166.9 ± 128.1 mg/L, while on Day 7 the concentrations decreased to a mean value of 42.7 ± 63.6 mg/L. The p-values for comparison with pre-operative values were: ($p<0.0005$), ($p<0.0005$), and ($p<0.005$) on post-operative Days 1, 2 and 7, respectively. There was a decline of 58.5% and 74.4% of CRP concentrations on post-operative Day 7 when compared with post-operative Day 1 and Day 2 respectively. Trends in the values for CRP post-surgery were similar in female and male patients. These observations do suggest that prolonged elevation may indicate an on-going infection.

Discussion

The aim of this study was to investigate the CRP value in pre- and post-operative serum samples in patients with brain tumours. Grouping the patients according to the duration of surgery, no significant difference in the mean serum CRP concentrations was observed in the study. This finding is consistent with a previous study which demonstrated no significant difference in the mean CRP concentrations for surgery lasting up to 5 hours with the exception of four patients in whom the concentrations of CRP were higher than for the rest of the group.¹⁷ CRP is known to be a sensitive indicator of infection and is involved in the acute phase reaction.^{1,2} Increased concentration of CRP even without signs of infection is considered a prognostic value after brain tumour surgery, which may itself result in a systemic inflammatory response syndrome (SIRS).¹⁸ SIRS is defined as the body's response to an infectious or non-infectious insult. It represents a clinical manifestation of inflammation, resulting in the activation of a normally quiescent system comprising components that including leucocytes, endothelial cells and cytokine networks.¹⁹ Elevated concentrations of CRP also have been demonstrated in patients with non-infectious SIRS, infectious SIRS (sepsis, severe sepsis and septic shock), or without SIRS.²⁰

However, normal CRP concentration in serum also does not exclude significant inflammation.²¹ These findings reflect the non-specificity of serum CRP measurement.

Major surgical procedures can cause extensive tissue damage, with local inflammation causing difficulty in the detection of post-operative bacterial complications. One of the most common and fatal complications after neurosurgery following a craniotomy is infection. In most cases the infection presents more than a week, after surgery, but in some it has presented even earlier. The diagnosis of infection is based on clinical findings and microbiological investigations which are required to identify the organism responsible and information about antibiotic resistance to help treatment. However, there are situations when clinical signs of infection may be masked, for example, in patients who are immunosuppressed.²¹ In these situations, markers of acute phase response and in particular, measurement of CRP concentrations in serum may be useful to give an independent marker of the presence of infection or inflammation.²¹

In this study, the pre-operative concentrations in most of the patients' CRP were normal i.e (<5). Out of five patients with elevated CRP concentrations, three had malignant (2 glioma and 1 lymphoma) and two had benign (meningioma) tumours. None experienced any signs of infection. Some studies indicate that patients with malignant extracranial tumours often display increased CRP pre-operative values,²² while others have shown CRP to be within the normal range in all brain tumour patients.¹⁷

Almost all post-operative patients who had raised serum CRP concentrations (>5mg/L) also showed no apparent infections. The rapid increase in CRP, peaking post-operatively on Day 2 and declining afterward, as observed in this study, suggests a normal physiological response of CRP after brain surgery. It is assumed that the underlying mechanisms, i.e. CRP synthesis in hepatocytes, is mainly induced by interleukin (IL-6), and also by IL-1 and TNF- α .^{2,3} In response to injury or infection, the above mechanism may trigger the synthesis of CRP.¹⁷

The data presented in this study suggests that the elevated concentrations of CRP in the serum of pre- and post-operative patients with no sign of infection most likely are an indicator of SIRS. This is consistent with the results of previous studies that showed elevated concentrations of CRP demonstrated in patients with non-infectious SIRS.²⁰ Furthermore, non-infectious SIRS can be secondary to tumour necrosis or local tissue damage caused by the malignant cells.^{23,24} It may also be caused by cytokine release from tumour cells that induce CRP.^{2,3}

It has also been reported that the serum concentrations of CRP invariably rise after major surgery, but they fall towards normal values over a period of 7-10 days.¹⁸ This study also demonstrated that the CRP value reaches a peak on the second post-operative day and declines afterward. We predict that an absence of this fall or a secondary rise in CRP from post-operative Day 7 would provide early warning of inter-current infection. Nevertheless, the elevated CRP concentrations in the post-operative period may not necessarily equate to infection, as observed in this study.

It is noted in the literature that different CRP peak values resulted from using different neurological procedures, with the peak ranging from 20.5mg/L¹⁷ to 75.0mg/L,^{17,25} which were strikingly different from our results i.e. 139.6 mg/L (range 10.3-463.9). This difference in CRP values might be due to the nature of the neurosurgical procedures that were carried out and caused an increase of CRP values or/and an increased sensitivity of the CRP method used in this study.

The limitation of the present study was its small sample size. It is also important to establish the normative data for the progression of serum CRP concentrations post-surgery (Day 1, Day 2 and Day 7) that may help differentiate increased values due to normal physiological response from postoperative infection.

Conclusion

The detection and identification of post-operative infections in patients undergoing brain tumour surgery is often difficult. The possibility of risk of imminent infection in patients after brain surgery is likely to occur only if there is no decline of CRP peak value from Day 2 or a secondary rise in CRP from post-operative Day 7 would provide early warning of inter-current infection. Furthermore, routine analysis of serum CRP, especially in high-risk patients, would be helpful in preventing infections or treating existing infections earlier and would help in reducing healthcare expenditure i.e. shortening the length of hospital stay.

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