

Serum CRP as a prognostic biomarker of delirium

Sunil Suthar¹, S. C. Tiwari², Anil Kumar³

¹ DM, Assistant Professor, Department of Psychiatry, Govt Medical College, Bharatpur, Rajasthan, India

² MD, Former Sr Professor, Department of Geriatric Mental Health, King George's Medical University, Lucknow, Uttar Pradesh, India

³ MD, Former Senior Resident, Department of Geriatric Mental Health, King George's Medical University, Lucknow, Uttar Pradesh, India

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Abstract

Introduction: Serum CRP (C-reactive protein) is frequently measured in clinical practice, but its clinical relevance with delirium is not well studied. **Aim:** To study clinical significance of serum CRP in relation to severity, mortality and long-term consequence of delirium (development of dementia). **Methodology:** Sixty five elderly patients (age \geq 60years) with delirium admitted in geriatric mental health department were recruited in this study. Underlying dementia was assessed using IQCODE-SF (Informant Questionnaire on Cognitive Decline-short form). Severity of delirium was assessed using DRS98-R (Delirium rating revised scale). Venous blood samples for serum CRP were collected on first day and seventh day of admission. Serum CRP levels were correlated with severity, duration of hospital stay, improvement, and mortality of delirium. Delirious patients without underlying dementia were followed up for 6 months for development of dementia and their cognition was assessed using HCST (Hindi cognitive screening test). **Results:** In seven days of admission delirium improved in 35 patients, while delirium didn't improve in 25 patients and 5 patients died. Serum CRP improved with improvement of delirium. (P= 0.001). No significant correlation found between serum CRP, severity of delirium and mortality. Serum CRP was significantly higher in delirious patients who developed dementia in compare to those who didn't develop dementia. **Conclusion:** Higher level of serum CRP in patients with delirium doesn't predict the severity of delirium and mortality, but it predicts the development of dementia in future.

Keywords: C-reactive protein, Serum, Delirium.

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Introduction

Delirium is a syndrome of Neurocognitive disorder characterised by disturbances in multiple domains such as consciousness, attention, ability to think clearly, ability to perceive external stimuli, psychomotor activity, sleep, emotions and memory[1]. Various biomarkers of delirium have been studied to understand neuropathophysiology of delirium and CRP is one of them.

C-reactive protein (CRP) is an acute phase protein produced by the liver and detected in serum is a systemic marker of inflammation. Higher levels of CRP lead to activation of astrocytes/microglia, neuroinflammation and disruption in blood brain barrier which in turn can lead to development of delirium[2]. In post-operative cases CRP level has been correlated with poor performance in cognition. CRP level predicts not only incidence but also recovery of delirium[3]. Lemstra, A. W. et al., didn't find any correlation between serum CRP level and development of delirium[4]. Study by George J et al., supports the role of CRP in delirium as marker for predicting recovery[5]. Serum CRP level is frequently measured in clinical practice while managing patients with delirium. But its significance in long term consequences of delirium such as risk of developing dementia is not studied. Therefore, this study was planned to study significance of serum CRP in short-term consequences of delirium (improvement in delirium and mortality) and long-term consequences of delirium (development of dementia).

*Correspondence

Dr. Sunil Suthar

Assistant Professor, Department of Psychiatry, Govt Medical College, Bharatpur, Rajasthan

E-mail: drsunilsuthar@gmail.com

Methodology

The study was carried out in a tertiary care hospital which caters to the geriatric population suffering from mental health issues. It was carried out between December 2015 and December 2016. Sixty-five elderly patients clinically diagnosed with delirium and admitted in department of geriatric mental health were recruited in this study. Diagnosis of delirium was made by geriatric mental health specialist using DSM-IV TR diagnostic criteria. A written informed consent was taken from the patient and/or primary care giver of the patients who met the inclusion and exclusion criteria. Inclusion criteria were age \geq 60 years, both male and female, and diagnosis of delirium. Exclusion criteria were presence of other chronic medical illness which may cause increase in CRP. For study purpose patients were examined clinically daily for seven days. If patients didn't meet DSM-IV TR diagnostic criteria for delirium for two consecutive days, they were labelled as delirium improved. On basis of improvement, patients were divided into two groups. Group 1 consisted of patients in whom delirium got improved in seven days and Group 2 consisted of patients in whom delirium didn't improve in seven days. Two venous blood samples were collected, first on the first day of admission and second on the seventh day. After collection samples were sent immediately to Department of Biochemistry for estimation of serum level of C-reactive protein. Serum CRP level estimations were done by dry chemistry analyser (J&J Vitros 250) and using colorimetric method. Severity of delirium was assessed using DRS-98 revised scale. Underlying dementia was assessed on day 1 using Informant Questionnaire on Cognitive Decline-short form (IQCODE-sf)[6]. On basis of IQCODE score patients were divided into two groups- 1) Delirium without dementia (IQCODE score $<$ 3.5) and 2) Delirium with dementia (IQCODE score \geq 3.5). Delirium without dementia group patients were followed for next six months and after six months cognition was

assessed using Hindi Cognitive Screening Test (HCST)⁷. The study was approved by the institutional ethics committee of the hospital.

Analysis

Socio-demographic data was expressed with the help of means and standard deviation. Difference in serum CRP on day 1 and day 7 was

expressed with the help of median and Z-score. For strength of association between serum CRP and different variables of delirium, correlation coefficient was used. A probability level of P<0.05 was considered significant.

Results

Table 1: Socio-Demographic Data

| | | |
|---------------------------------------|----------------------------------|------------|
| Mean age (Years) | | 74.9+-8.7 |
| Sex | Male | 39 (65%) |
| | Female | 21 (35%) |
| Marital Status | Single | 3 (5%) |
| | Married | 34 (56.7%) |
| | Widow/Widower | 23 (38.3%) |
| | Divorced/Separated | 0 |
| Religion | Hindu | 51 (85%) |
| | Sikh | 1 (1.7%) |
| | Muslim | 8 (13.3%) |
| | Others | 0 |
| Educational Status | Illiterate | 19 (31.7%) |
| | Primary | 14 (23.3%) |
| | Middle | 4 (6.7%) |
| | Secondary | 5 (8.3%) |
| | Inter | 9 (15%) |
| | Diploma | 0 |
| | Graduate | 4 (6.7%) |
| | Post-Graduate | 5 (8.3%) |
| | Doctorate | 0 |
| | Unknown | 0 |
| Family Type | Nuclear/Extended Nuclear | 36 (60%) |
| | Joint | 24 (40%) |
| | Others | 0 |
| Locality | Urban | 27 (45%) |
| | Rural | 33 (55%) |
| Occupation | Unemployed(including Housewives) | 35 (58.3%) |
| | Employed | 7 (11.7%) |
| | Retired | 18 (30%) |
| Monthly Income in rupees (per capita) | Nil-5000 | 28 (46.7%) |
| | 5001-10000 | 16(26.7%) |
| | 10001-15000 | 8 (13.3%) |
| | 15001-20000 | 5 (8.3%) |
| | >20000 | 3 (5%) |
| Dementia | Present | 21 (35%) |
| | Absent | 39 (65%) |

Mean age of all patients with delirium were- 73.9 ± 7.7. At the time of admission 26 patients were having underlying dementia. In thirty-five patients delirium improved within seven days.

Table 2: Serum CRP level (mg/l) on day 1 and day 7 in patients whom delirium improved (N=35)

| | CRP (mg/dl) | Median | Z score | P Value |
|--------------------------|-------------|-----------------|---------|---------|
| Delirium Improved (N=35) | Day-1 | 7.0 (2.0-24.30) | -3.56 | 0.001 |
| | Day-7 | 3.5 (1.3-6.0) | | |

CRP level declined with improvement in delirium and this decline was statistically significant (P= 0.001).

Table 3: Serum CRP level (mg/l) on day 1 and day 7 in patients whom delirium not improved (N=35)

| | CRP(mg/dl) | Median | Z-score | P Value |
|------------------------------|------------|-----------------|---------|---------|
| Delirium not improved (N=25) | Day-1 | 13.8 (2.9-82.1) | -2.91 | 0.101 |
| | Day-7 | 10.0 (1.8-57.0) | | |

Serum CRP didn't decline significantly in patients whom delirium didn't improve in seven days.

Table 4: Serum CRP level in patients who survived and died in 7 days of delirium

| | Mean | P value |
|--------------------------|-----------------|---------|
| Patients survived (n=60) | 7.0 (2.0-24.30) | 0.21 |
| Patients died (n=5) | 6.9 (5-20.7) | |

On comparing baseline serum CRP level in patients with delirium who survived and died, no significant difference was found.

Table 5: Correlation of serum CRP level on day-1 with various parameters of delirium

| | Serum CRP level | |
|--------------------------------------|-------------------------|---------|
| | Correlation coefficient | P Value |
| Severity of delirium (DRS-98R score) | 0.034 | 0.737 |
| Duration of hospital stay | 0.044 | 0.738 |

No significant correlation was found between serum CRP level and severity of delirium and hospital stay.

Thirty-nine delirious patients without underlying dementia were followed for next 6 months. 4 patients lost the follow-up (3 died and 1 didn't reported). Among rest of 35 patients, 10 developed dementia (HCST<23) while 25 were having normal cognition (HCST ≥24).

Table 6: At the end of 6-month follow-up of patients with delirium but without underlying dementia

| | CRP level at the time of admission | P value |
|--------------------------------|------------------------------------|---------|
| Developed dementia (N=25) | 8.1 (3.0-18.9) | 0.03 |
| Didn't develop dementia (N=10) | 5.7 (1.8-12.9) | |

Baseline serum CRP level was significantly higher in patients who developed dementia. (P=0.03)

Discussion

CRP plays role in pathophysiology of delirium. In this study, serum CRP level significantly declined with improvement of delirium. Which suggest possible role of CRP in pathophysiology of delirium. Similarly in previous studies Macdonald A et al., has studied association between improvement of delirium and improvement in CRP level and found that association between CRP and incident delirium was stronger than with improvement in delirium[3]. On further exploring the relationship of CRP with other clinical parameters, No significant association found between serum CRP level and severity of delirium. Correlation between serum CRP level and duration of hospital stay was also not significant. Similarly, Ritchie, C et al., found that level of CRP was not associated with severity of delirium[2]. On six months follow-up 10 out of 35 cases of delirium developed dementia. On comparing baseline CRP level, it was significantly higher in patients those who developed dementia. Therefore, baseline higher serum CRP can be used a predictor of dementia.

Conclusion

Serum level of CRP in patients with delirium doesn't predicts severity, duration of hospital stay, and mortality. But higher level of CRP in patients with delirium predicts development of dementia in future. Therefore, clinician should be cautious while managing the patients with delirium who have higher level of serum CRP.

Conflict of Interest: Nil

Source of support: Nil

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