C-Reactive Protein Levels in Patients with Infectious Mononucleosis

Alon Nevet (✉ alon.nevet@gmail.com)

Hillel Yaffe Medical Center <https://orcid.org/0000-0002-0922-2166>

Maanit Shapira

Hillel Yaffe Medical Center

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Abstract

Background: Plasma level of C-reactive protein (CRP) is used as a biomarker of systemic inflammation. Differential distributions of CRP levels related to different pathogens aid clinicians in the differential diagnosis of patients.

Objectives: To evaluate the distribution of CRP levels in patients with Infectious Mononucleosis (IMN) and its correlation with different pathogen and host characteristics.

Methods: A retrospective study conducted on electronic medical records of patients diagnosed clinically and serologically with IMN in a public regional hospital during consecutive five years.

Results: CRP levels were significantly elevated in patients hospitalized with clinical diagnosis of IMN and serologic evidence of EBV (average 6.8 md/dL) or CMV (average 6.3 md/dL). However, levels of CRP were not significantly correlated with plasma levels of liver enzymes.

Conclusions: Although CRP levels may aid in the differential diagnosis of respiratory syndromes, its distribution in patients infected by hepatotropic viruses is similar to that in bacterial infections.

Introduction

C-reactive protein (CRP) is part of the complementary chain of reactions in response to inflammation-provoking triggers. It is produced in the liver, and secreted to the blood plasma, where its levels are routinely measured.

Due to the statistically higher levels of CRP correlated with bacterial infections relative to respiratory viruses, different cutoffs have been proposed to assist clinicians in the differential diagnosis of systemic inflammation [1–4].

However, some viral infections and non-infectious states are associated with CRP levels overlapping those induced by bacterial infections [5].

Specifically, high CRP levels were demonstrated to be associated with Herpetic and Adenoviral infections. These viruses are hepatotropic, thus may directly stimulate the production of CRP in the liver.

To further examine the association between hepatotropic viral infections with elevated CRP levels, we examined its levels in patients with infectious mononucleosis (IMN), caused by Cytomegalovirus (CMV) or Epstein-Barr Virus (EBV), and the correlation between CRP and liver enzymes levels in these patients.

Patients And Methods

The study was conducted retrospectively on electronic health records of inpatients diagnosed with IMN using the combination of clinical symptoms and positive serology between January 2014 and December

2018 in Hillel Yaffe Medical Center, a regional public hospital.

Only records with data regarding CRP and liver enzymes were included, and those with positive bacterial cultures were excluded.

Results

Sixty five patients were included in the study, as described in Table 1.

Virus	Male	Female	Age (Average)
EBV	35	22	22 - 84 (46.3)
CMV	1	7	1 - 52 (15.9)
TOTAL	36	29	1 - 84 (42.6)
EBV – Epstein Barr Virus; CMV - Cytomegalovirus			

Table 1: Demographics

The average CRP level was 6.1 mg/dL (CMV patients 6.3 mg/dL, EBV patients 6.0 mg/dL). Twenty four patients (37%) had CRP levels higher than 5 mg/dL, which are considered indicative of bacterial infection in certain clinical scenarios, such as respiratory infections.

As expected, liver enzymes were elevated in most patients (ALT>35 U/L in 55% of patients, average 94.6 U/L). However, CRP and ALT levels were not significantly correlated with each other, nor with age.

Discussion

This study demonstrates that elevated levels of CRP are found in a significant portion of patients hospitalized with IMN without bacterial co-infection.

The mechanisms underlying the induction of CRP synthesis in different circumstances are still to be explored. Cytokines such as interleukin-6 and tumor necrosis factor-alpha have been shown to be involved [6–10], but their relation to specific characteristics of the offending microorganism is unknown. Exceptionally high levels have been reported in patients with adenovirus [2, 11] and herpes simplex virus (HSV) infections [12].

Since adenovirus and HSV are hepatotropic viruses, and CRP is synthesized in the liver, our hypothesis was that the distribution of CRP levels would be similarly elevated in patients infected by other hepatotropic viruses - EBV and CMV. The results presented in the current study support the hypothesis of a general relation between hepatotropic viral infections and elevated CRP levels, relative to historic cohorts of patients with respiratory virus infections [13], and similar to bacterial infections.

Although CRP may support clinical decisions when the differential diagnosis includes viral and bacterial infections, the extent of its application is controversial[13–16] due to the relatively high gap between specificity and sensitivity, independent of the threshold used. This gap is the result of overlap between CRP values distribution related to different conditions.

Our results may aid clinicians by suggesting that elevated CRP levels in a clinical context implying infection caused by hepatotropic viruses (e.g. conjunctivitis for adenovirus, oral aphtha for HSV, rash, lymphadenopathy and/or elevated liver enzymes for IMN) do not necessarily indicate bacterial co-infection, and antibiotic therapy may be withheld.

However, CRP remains important in patients lacking clinical signs and laboratory results implying a possible hepatotropic viral infection. In the relevant clinical scenarios, such as fever without localizing signs or patients with pneumonia, CRP levels of 5 mg/dL and above support the possibility of bacterial infection and decisions to initiate empirical antibiotic therapy [2, 4, 13, 14].

To the best of our knowledge, this work is the first to systematically evaluate CRP values in patient with IMN. The retrospective nature of this work and the characteristics of its population preclude definitive conclusions regarding the distribution of CRP among IMN patients in the community. However, even if the results refer to a subpopulation of IMN patients, the general conclusions and recommendations presented above remain relevant.

Declarations

- *Ethics approval and consent to participate:*

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Hillel Yaffe Medical Center (HYMC 87-19). This is an observational study. The Research Ethics Committee has confirmed that informed consent is not required.

- *Consent for publication:*

Not Applicable

- *Availability of data and materials:*

The dataset will be sent by request.

- *Competing interests:*

The authors have no relevant financial or non-financial interests to disclose.

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- *Authors' contributions:*

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Alon Nevet and Maanit Shapira. The first draft of the manuscript was written by Alon Nevet and Maanit Shapira commented on previous versions of the manuscript. Both authors read and approved the final manuscript.

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