Very High CRP: Associated Diseases and Possible Diagnostic Value

Dr. Emad A. Koshak, FRCPC, Dr. Aisha A. Alghamdi, FACP
Faculty of Medicine-King Abdulaziz University Hospital - Jeddah, Saudi Arabia

Background: C reactive protein (CRP) is the classical acute-phase reactant involved in host immunity. Although it can increase up to 1,000 fold in response to inflammation, the diagnostic value of very high levels of CRP (vhCRP) is not known. Objective: To explore any diagnostic value of vhCRP through investigating the spectrum of associated diseases in patients at King Abdulaziz University Hospital (KAUH).

Method: Over a year period, CRP tests performed by immunonephelometry were sequentially collected from the laboratory of clinical immunology at KAUH. Tests with vhCRP were arbitrarily identified as those with CRP levels 100 mg/l. Their charts were reviewed for demographic and clinical data.

Results: A total of 720 CRP tests were collected. CRP levels were elevated (≥10 mg/l) in 494 tests (68.8%). VhCRP levels were detected in 107 tests (15%), and only charts of 97 different tests (13.55) were found. In these, VhCRP were elevated up to 391 mg/l (mean 184 +SD 66). The study group's age ranged between 1 - 88 years old with a mean of 28 +SD23, and females constituted 51% of them. The most common diagnoses category associated with vhCRP was infectious diseases (70%), followed by rheumatological diseases (21%). In the infectious diseases, the most frequent diseases were pneumonia (14%) and septicemia (14%). There was a significant like-hood ratio between vhCRP and the category of infectious diseases (df=74, P<0.05).

Conclusion: Elevation of CRP is a common inflammatory immune response in patients at KAUH. This advocates its use as a sensitive marker in screening for illnesses with inflammation. Although this study did not reveal any diagnostic value of vhCRP regarding any specific disease, vhCRP might be a useful parameter in differentiating diseases with infectious pathology.

CRP was identified in 1930, and its serum levels are elevated in a wide variety of acute and chronic inflammation (1, 2). It was subsequently considered to be an "acute phase protein" which acts as an early indicator of many inflammatory conditions (3, 4).

CRP belongs to the ß-globulin family of human plasma proteins and derives its name from its ability to precipitate a group C polysaccharide of pneumococcus in the presence of Ca2+ (1). CRP binds to a range of substances and is a ligand for specific receptors on phagocytic leukocytes, mediates activation reactions on monocytes and macrophages, and activates complement (5). Hence, CRP is classified as an

effector of innate host resistance because it helps in opsonisation and activates the classical complement cascade (6).

Recently, improved laboratory methods for quantifying CRP with high sensitivity assay have led to the increased application to clinical medicine (7, 8). CRP can increase to very high levels up to 1,000-fold in response to infection, ischemia, trauma, burns, and inflammatory conditions, which represent a huge range of illnesses seen in any hospital (5). Diseases associated with very high CRP (vhCRP) levels, which might help in their diagnosis and prognosis, have not been explored in the literature.

In our area, local studies to establish normal range of CRP have not yet been established

Such vhCRP levels are frequently encountered in the sera of some patients seen at King Abdulaziz University Hospital (KAUH). KAUH, with its 420 beds, is a teaching hospital and a tertiary care medical centre. Hence, the present study was conducted to determine any possible diagnostic value of vhCRP through exploring the spectrum of associated diseases in the cases seen at KAUH.

Methods

Candidates and samples:

Requests for CRP assessment on sera of patients sent to the clinical immunology laboratory at KAUH over one year were sequentially collected. The period of the study was from January 2000 to December 2000. Blood specimens were collected in tubes using standard venipuncture techniques. The serum samples must be completely coagulated and, after centrifugation, must not contain any particles or traces of fibrin.

CRP measurement:

Over the last few years, a new high sensitive immunoassay technique for the measurement of CRP has been introduced in clinical immunology laboratories (7). Such new technology is called high sensitivity CRP (hs-CRP) and is currently used for routine CRP assessment.

hs-CRP is an in vitro diagnostic assay indented for the quantitative determination of CRP in human serum by means of particle-enhanced immunonephelometry using BN II system by Dade Behring®. Polystyrene particles coated with monoclonal antibodies to CRP are agglutinated when mixed with samples containing CRP. The intensity of the scattered light in the nephelometer depends on the CRP content of the sample and therefore the CRP concentration can be determined versus dilutions of a standard of a known concentration.

According to international references, normal range of CRP levels is variable. In healthy young adult volunteer blood donors, the median concentration of CRP is 0.8 mg/l, the 90th centile is 3.0 mg/l, and the 99th centile is 10 mg/l (9). The term vhCRP is not well stated in the literature. In our area, local studies to establish normal range of CRP have not yet been established. In one reference, a CRP level between 10 and 100 mg/l is considered a moderate elevation and above 100 mg/l is a marked elevation (10). In this study, the cut-off level for vhCRP cases were arbitrarily defined as those with CRP serum levels of equal to or more than 100 mg/l of peripheral blood.

Patients with vhCRP who fulfill the above criteria were selected, and their files were retrieved from the medical record department. These files were extensively reviewed retrospectively by the researchers who were to record the demographic data and the most active diagnosis during the CRP sample. Associated illnesses diagnoses were grouped into diagnostic categories as close to the different etiologies of increased CRP by the system involved.

Data analysis:

The data was entered into a personal computer and the statistical analysis was performed using the SPSS statistical package software (version 11). The Chi-square test and Anova correlation were used for exploring any significance.

Results

Over a one-year period, a total of 720 tests of CRP were collected. Abnormal CRP levels (equal or more than 10 mg/l) was elevated in 488 tests that account for 68.8% of all studied samples.

VhCRP levels of equal or more than 100 mg/l were found in 120 tests (16.7%). Of these, thirteen tests were excluded because of repeated file numbers. This leaves 107 different tests of vhCRP which account for 15% of all samples. The files of ten tests could not be found in the medical records. Thus, only a total of 97 tests of vhCRP (13.5% of all cases) were included in the study. The levels of these VhCRP tests ranged between 100 - 391 mg/l with a mean of 184 +SD66. Their ages ranged between 1 - 88 years old with a mean of 28 +SD23. Females constituted 51% of the studied cases and 57% of cases were Saudi nationals.

The most frequent diagnostic categories associated with vhCRP were infectious diseases in 70%, followed by rheumatological diseases in 21% and malignancy diseases in 7%. The frequency of other diagnostic categories and the spectrum of diseases associated with each category are demonstrated in table-1. Additionally, the ranges and means of vhCRP in each of these diagnostic categories are also shown in table-1. By using the Chi-Square test, the likehood ratio for vhCRP was significantly associated with the category of infectious disorders ($df=74$, $P<0.05$).

Among the infectious diseases, the predominant diagnoses were pneumonia in 14 tests and septicemia in 14 tests (each account for 21% of all the infectious diseases). Among the rheumatological diseases, the predominant diagnoses were rheumatoid arthritis in 5 tests and rheumatic fever in 5 tests (each account for 25% of all the rheumatological dis-

Diseases categories	Freq	Percent	VhCRP Range	VhCRP Mean ±SD
Infectious diseases	68*	70	100-380	179±64
Pneumonia	14	14.4	102-380	196±90
Septicemia	14	14.4	109-275	185±46
Osteomyltitis	8	8.2	133-288	179±54
Septic arthritis	7	7.2	100-162	124±22
Pulmonary Tuberculosis	6	6.2	113-230	166±47
Cellulitis	5	5.2	156-308	216±64
Pyelonephritis	4	4.1	158-316	218±66
Brucellosis	3	3.1	100-201	149±51
Tonsilitis	3	3.1	128-146	139±9
Endocarditis	2	2.1	152-312	232±113
Meningitis	2	2.1	101-192	147+64
Rheumatological diseases	20	21	111-391	186±72
Rheumatoid arthritis	5	5.2	112-173	133±25
Rheumatic fever	5	5.2	119-180	152±26
SLE	4	4.1	182-391	277±102
Juvenile Rheumatoid arthritis	4	4..1	111-209	163±45
Tachiasu artritis	1	1	250	-
Antiphospholipids syndrome	1	1	252	-
Malignancies	7	7	118-284	199±64
Leukemia	4	4.1	118-284	222±79
Lymphoma	1	1	189	-
Renal cell carcinoma	1	1	149	-
Multiple myloma	1	1	169	-
Neurology (Cerebrovascular accident)	1	1	275	-
Cardioology (Myocardial infarction)	1	1	199	-
Total	97	100	100 - 391	184 ±66

* Statistical significance (df=74, P<0.05)

Figure 1 - Diagnostic categories and diseases associate with vhCRP

eases). Among the malignant diseases, the predominant diagnosis was leukemia in 4 tests (57% of malignancies). There was no significant association among vhCRP and any of the studied diseases. Of all the studied cases with vhCRP, fourteen died with a mortality rate of 14.4%.

Discussion

Assessment of laboratory values is an important function of health care providers practice. This study was designed to assess the spectrum of diseases associated with very high serum CRP concentrations in the sera of cases seen in KAUH and to explore any possible diagnostic value of such high levels. Abnormally elevated CRP levels were a common finding at the patients of this university hospital (more than 68.8%). This might make the CRP test a sensitive tool for screening for illnesses. Since its discovery, CRP has been studied as a screening device for inflammation, a marker for disease activity, and as a diagnostic adjunct (2, 5). The assay of CRP is a more sensitive and more reliable indicator of acute inflammatory processes than the erythrocyte sedimentation rate (ESR) and the leukocyte count (11, 12). Only those interventions affecting the inflammatory process responsible for the acute phase reaction can change the CRP level.

In this study, VhCRP levels of more than 100 mg/l were detected in 15 % of the studied cases. They were from the spectrum of all ages and both sexes. The most frequent diagnostic categories associated with vhCRP were infectious diseases in 68% of all cases. In the literature, both acute systemic Gram-positive and Gram-negative bacterial infections are among the most potent stimuli for CRP production (13, 2). CRP binds to several polysaccharides and peptido-polysaccharides present in bacteria, fungi, and parasites in the presence of calcium. These complexes activate the classical complement pathway, which is one of its main mechanisms in providing host defense (14). It has recently been recognized that C-reactive protein interacts with the cells of the immune system by binding to Fc gamma receptors. It may thus bridge the gap between innate and adaptive immunity and provide an early effective antibacterial response (15).

Among the infectious disorders found in this study, the predominant diagnoses were pneumonia in 21% of the cases and septicemia in another 21% of them, followed by other types of infections. CRP is frequently used in hospitalized patients as a sepsis marker (16). Previous studies revealed that bacterial pneumonia, particularly pneumococcal, is a more severe illness than the serologically diagnosed one and are usually associated with high mean CRP (7, 17). However, CRP has no role in diagnosing any clinical entity, and a normal CRP level should never delay antibiotic coverage. In critically ill patients, another inflammatory marker is currently under focus and that is the admission procalcitonin concentration which is advocated as a better diagnostic marker of infection than CRP or leukocyte count (18).

In this study, the second most frequent

diagnostic categories associated with vhCRP were rheumatological disorders and found in 21% of the cases. In the rheumatological disorders, the predominant diagnoses were rheumatoid arthritis in 25% of the cases and rheumatic fever in another 25% of them. The other common rheumatological diagnoses are also detected and are listed in table-4. CRP is commonly elevated in such disorders and may be used in monitoring disease activity, but there is no significant correlation between vhCRP and any specific rheumatological diagnosis (11, 19). Rheumatologic laboratory assessment can be complex because few findings are actually pathognomonic (20, 21). An interpretive approach to laboratory assessment of rheumatologic disease in conjunction with the patient's clinical status may provide helpful information for monitoring or predicting the course of disease (20, 21).

It is hard to see how the results of this study might be used. It is not clear what the original indication for the CRP was. Clearly, this test was done on a particular subset of patients and it is not clear whether the test was ordered to help with the diagnosis or to serve as a guide to the subsequent response to therapy. Certainly, improper use and interpretation of CRP test results can lead to incorrect diagnosis and unnecessary therapy, and potentially putting the patient at risk (21). Thus, these tests should be ordered in the context of other clinical information that provides the practitioner with an accurate estimate of disease probability.

Of all vhCRP cases, the mortality rate was 14%. Some studies have revealed that elevated concentrations of serum CRP are correlated with an increased risk of organ failure and death (5, 16). Moreover, persistently high CRP concentrations are associated with a poor outcome and serial measurements may be helpful to identify those patients who require more aggressive interventions to prevent complications (16). In conjunction with the patient's clinical status, these values may provide helpful information for monitoring or predicting the course of disease (21).

Inflammation markers have been related to cardiovascular short and long-term prognosis (22, 23). Recent evidence has indicated that CRP is an important risk factor for cardiovascular disease (24, 25). CRP appears to be a multifunctional protein with the capability of exerting both effector functions for innate host resistance as well as exerting specific anti-inflammatory effects (6). However, further studies are needed to determine its long-term prognostic value.

In conclusion, CRP is a common marker of inflammation and potentially can be utilized as a sensitive laboratory tool in screening for inflammatory illnesses. Very high levels of CRP might be used as a useful parameter in differentiating and monitoring diseases with infectious pathology. However, CRP levels must be interpreted in the clinical context; no single value can be used to rule in or rule out a specific diagnosis.

REFERENCES

1. Pepys, MB, Baltz, M.L. Acute Phase Proteins With Special Reference To C-Reactive Protein And Related Proteins (Pentaxins) And Serum Amyloid A Protein. Adv. Immunol (1983), 34, 141 212
2. Kind CRH, Pepys MB. The Role of Serum C-Reactive (CRP) Measurement in Clinicl Practice. Int Med 1984; 5:112-151.
3. Kushner I, Rzewnicki DL. The Acute Phase Response: General Aspects. Baillière's Clinical Rheumatology 1994; 8:513-530.
4. Young B, Gleeson M, Cripps AW. C-Reactive Protein: A Critical Review. Pathology 1991; 23:118–124.
5. Westhuyzen J, Healy H. Review: Biology and Relevance of C-Reactive Protein In Cardiovascular And Renal Disease. Ann Clin Lab Sci 2000 Apr; 30(2):133-43.
6. Mortensen RF, Zhong W. Regulation of Phagocytic Leukocyte Activities by C-Reactive Protein. J Leukoc Biol 2000 Apr; 67(4):495 500.
7. Rifai N, Tracy RP, Ridker PM. Clinical Efficacy of an Automated High-Sensitivity C-Reactive Protein Assay. Clin Chem 1999 Dec; 45(12):2136-41.
8. Clyne B, Olshaker JS. The C-Reactive Protein. J Emerg Med 1999 Nov-Dec; 17(6):1019-25.
9. Shine, B., de Beer, F.C., & Pepys, M.B. Solid Phase Radioimmunoassays for C-Reactive Protein. Clin. Chim. Acta (1981), 117, 13 23.
10. Gardner GC, the University of Washington school of medicine. http://uwcme.org/courses/rheumatology/rheumlab/crp.html. 1996.
11. Dixon JS, Bird HA, Sitton NG. C-Reactive Protein In The Serial Assessment Of Disease Activity In Rheumatoid Arthritis. Scand J Rheum 1984; 13:39-44.
12. Gambino R. C-Reactive Protein: An Underutilized Test. Lab Report for Physicians 1989, 11:41-44.
13. Pepys MB. C-Reactive Protein: Fifty Years On. Lancet 1981; 1:653-357.
14. Du Clos, Terry W. Functions of C-Reactive Protein. Ann Med 2000; 32:274-278.
15. Du Clos TW, Mold C. The Role of C-Reactive Protein In The Resolution Of Bacterial Infection. Current Opinion In Infectious Diseases 2001; 14:289-293.
16. Lobo SM, Lobo FR, Bota DP, Lopes-Ferreira F, Soliman HM, Melot C, Vincent JL. C-reactive protein levels correlate with mortality and organ failure in critically ill patients. Chest. 2003 Jun; 123(6):2043-9.
17. Hedlund J, Hansson LO. Procalcitonin and C-Reactive Protein Levels in Community-Acquired Pneumonia: Correlation with Etiology And Prognosis. Infection 2000 Mar-Apr; 28(2):68-73.
18. Hatherill M, Tibby SM, Sykes K, Turner C, Murdoch IA. Diagnostic Markers Of Infection: Comparison Of Procalcitonin With C-Reactive Protein And Leucocyte Count. Arch Dis Child 1999 Nov; 81(5):417-21.
19. van Leeuwen M, van Rijswijk MH. Acute Phase Proteins In Monitoring Of Inflammatory Disorders. Baillière's Clinical Rheumatology 1994; 8:531-552.
20. Rothschild BM, Rothschild C, Miller MA. Laboratory Aspects Of Rheumatologic Disease. Nurs Clin North Am 2000 Mar; 35(1):287-94.
21. Kavanaugh A. The Role Of The Laboratory In The Evaluation Of Rheumatic Diseases. Clin Cornerstone 1999;2(2):11-25.
22. Buffon A, Liuzzo G, Biasucci LM, Pasqualetti P, Ramazzotti V, Rebuzzi AG, Crea F, Maseri A. Preprocedural Serum Levels Of C-Reactive Protein Predict Early Complications And Late Restenosis After Coronary Angioplasty. J Am Coll Cardiol 1999 Nov 1; 34(5):1512-21.
23. Feng D, Tracy RP, Lipinska I, Murillo J, McKenna C, Tofler GH. Effect Of Short-Term Aspirin Use On C-Reactive Protein. J Thromb Thrombolysis 2000 Jan; 9(1):37-41.
24. Pepys, MB, Hirschfield GM. C-Reactive Protein: A Critical Update. J Clin Invest. 2003 June 15;111(12):1805–1812.
25. Aronow WS. C-Reactive Protein. Should It Be Considered A Coronary Risk Factor? Geriatrics. 2003;58(5):19-25.