Evaluation of C-reactive protein titer in patients with acute hepatitis B virus infection

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Abstract:

Objective: to evaluate the serum C-reactive protein (CRP) titer as a predictive diagnosis of acute hepatitis B virus (HBV) infection.

Materials and methods: One hundred and five patients with acute HBV infection and 117 apparently healthy individuals as a control group were enrolled in this study. The patients include 37(35.2%) females and 68 (64.8%) males with mean age (27±16.5) years. The control group includes 57 (48.7%) females and 60 (51.3%) males with mean age (26±5.8) years. Blood samples were collected, sera were separated and stored at -20 ^{0}C. The diagnosis of acute HBV infection was based on detection of HBS Ag and anti-HBc IgM and standard liver function tests. Determination of CRP titer was assessed by semi-quantitative tube agglutination test. All data were statistically analyzed.

Results: Based on 95% percentile, the baseline CRP titer in healthy individuals was 1:8 (16 mg/l) and for patients 1:512 (1024 mg/l). There was a statistically significant increase in the mean CRP titer in patients with acute HBV infection compared to healthy individuals (P< 0.001). The validy of CRP titer 1:64 as a cut-off value to predict HBV infection provide a sensitivity and specificity 100% and 96% respectively. The positive and negative predictive values were 95% and 100% respectively with an accuracy of 98%. Furthermore, there was a significant correlation between CRP titer and liver function test values.

Conclusion: In conjunction with clinical suspicions, CRP titer may be of value for predictive diagnosis of acute hepatitis B infection.

Key words: C-reactive protein, Hepatitis B virus.

Introduction:

C-reactive protein is a non-glycosylated polymeric protein belong to the pentraxin family of calcium-dependent ligand-binding plasma protein. Plasma CRP is produced only by hepatocytes predominantly under control of interleukin 6 (IL-6), although other sites of local synthesis have been suggested [1]. CRP production is part of non-specific acute-phase response to most forms of inflammation, infection, and tissue damage [2]. It has been suggested that the sole determinant of circulating CRP concentration is the synthesis rate, which thus directly reflects the intensity of the pathological processes stimulating CRP production [3].

During the past few years, it has repeatedly shown that CRP is a strong predictor of cardiovascular disease [4-6],diabetes mellitus and hyperlipidemia [7,8] and various bacterial infection particularly septicemia [9,10].

Materials and methods:

One hundred and five patients with acute HBV infection and 117 apparently healthy individuals as a control group were collected by simple random technique. This study was conducted from 1st.October 2003 to 30th. August 2004. The patents include 37(35.2%) females and 68 (64.8%) males with mean age (27 16.5) years. The control group include 57 (48.7%) females and 60 (51.3%) males with mean age (26 5.8) years. Blood samples were collected; sera were separated and stored in aliqutes at -20 ^{0}C till use. The diagnosis of acute HBV infection was based on detection of HBs Ag and anti-HBc IgM and standard liver function tests [Total, direct, and indirect serum bilirubin, Alanine aminotransferase (ALT), Alanine aspartate aminotransferase (AST), total serum protein, serum alkaline phosphatase]. Determination of CRP titer was assessed by semi-quantitative tube agglutination test. All data were statistically analyzed using computerized SSP version 13.

Results:

Table (1) showed that 41 (35%) of the healthy control had the lowest CRP titer (zero), while the highest titer (1:16) was found in 5(4.3%). The 95% percentile of CRP titer was 1:8. In patients, the lowest titer 1:16 was found in 4(3.8%) and the highest titer 1:1024 was found in 2(1.9%). The 95% percentile of CRP titer was 1:512. The mean CRP titer in healthy control was 1:8, while the mean titer in patients with acute HBV infection was 1:64.

Table (1): C - reactive protein titer in patients with acute HBV infection and controls

CRP titer	Healthy control		Patients	
	No.	%	No.	%
0	41	35	0	0
2	24	20.5	0	0
4	19	16.3	0	0
8	28	23.9	0	0
16	5	4.3	4	3.8
32	0	0	25	23.8
64	0	0	27	25.7
128	0	0	24	22.9
256	0	0	13	12.4
512	0	0	10	9.5
1024	0	0	2	1.9
Total	117	100	105	100
95% percentile	112(95.7)		103 (98.1)	

Table (2) showed the range, median and interquartile range of CRP titer in the study groups. The statistical analyses (Mann-Whitney test) revealed a significant difference in the median of CRP titer between the two study groups.

The validity of CRP titer 1:8 as a cut-off value to differentiate between healthy control and patients with acute HBV infection when clinical suspicion was 50%. The results showed that all patients give a titer 1:8 and more, whereas, 84 of the healthy control give a titer > 1:8 and 33 of them gives a titer 1:8 and more. The statistical analysis showed a significant difference between the two groups (P > 0.001). The sensitivity and specificity of the test were 100% and 72% respectively. The positive and negative predictive values were 76% and100% respectively. The test accuracy was 85%. Table (3).

Table (2): Range, median and interquartile range of CRP titer in study groups

CRP titer	Healthy control	Patients
Range	(0-16)	16-1024
Median	2	64
Interquartile range	(0-8)	(32-256)

P (Mann-Whiney) < 0.001

Table (3): validity of CRP titer at 1:8 as a cut-off value

CRP titer at cut-off 8	Healthy control	Patients	P value
Negative < 1:8	84	0	< 0.001
Positive 1:8 and more	33	105	
Total	117	105	

Sensitivity = 100% Specificity = 72% Positive predictive value = 76%
negative predictive value = 100% Accuracy = 85% False positive = 28% False negative = 0%

The validity of CRP titer at 1:16 as a cut-off value revealed that 112 of the healthy control give a titer > 1:16, while the remaining 5 gives a titer 1:16 and more. On the other hand, all patients give a titer 1:16 and more. There was a statistically significant difference between the two groups (P> 0.001). The sensitivity and specificity were 100% and 96% respectively. The positive and negative predictive values were 95% and 100% respectively. The accuracy was 98%, table (4).

Although there was no significant correlation between the CRP titer and liver function tests (total, direct, indirect serum bilirubin, ALT, AST, Total serum protein and serum alkaline phosphatase) in the healthy group as assessed by Spearman's linear correlation. However, the CRP titer was highly correlated with liver function tests in patient group, table (5).

Table (4): validy of CRP titer at 1:16 as a cut-off value

CRP titer at cut-off 16	Healthy control	Patients	P value
Negative < 1:16	112	0	< 0.001
Positive 1:16 and more	5	105	
Total	117	105	

Sensitivity = 100% Specificity = 96% Positive predictive value = 95%
Negative predictive value = 100% Accuracy = 98% False positive = 4% False negative = 0%

Table(5): Spearman's linear correlation between CRP and liver function tests

Liver function test	Spearman's linear correlation			
	Control		Acute hepatitis B	
	r	P value	r	P value
S. Alkaline phosphatase	-0.07	0.48 [NS]	0.24	0.013
SAST	- 0.09	0.34 [NS]	0.47	< 0.001
S ALT	- 0.03	0.72 [NS]	0.45	< 0.001
Total serum protein	- 0.01	0.93 [NS]	0.60	< 0.001
Total serum bilirubin	- 0.06	0.51 [NS]	0.57	< 0.001
Indirect serum bilirubin	- 0.06	0.52 [NS]	0.44	< 0.001
Direct serum bilirubin	-0.02	0.83 [NS]	0.53	< 0.001

Discussion:

C-reactive protein is a test which measures the concentration in serum of a special protein produced in the liver that is present during episodes of acute inflammation or infection. In the body, CRP plays the important role of interacting with the complement system, an immunologic defense mechanism [11].

Hepatitis is an inflammation of the hepatocytes. Viral infections are among the most common cause of hepatitis [12,13]. Hepatitis B virus infection is the most common cause of acute viral hepatitis [14]. Hepatitis B virus infection is endemic in Iraq, The chronicity rate among healthy blood donors in Diyala province is 1.6% [15].

The mean serum CRP concentration in healthy subjects obtained in the present study was relatively higher than that reported by Shaya et al. (2002)[16] in Al-Ramadi city who found that the CRP concentration among apparently healthy subjects was 6 mg/l. This may be due to the presence of asymptomatic infectious and/ or non-infectious disease that may have a role in elevating the CRP concentration. However, it is generally agree that a CRP concentration above 10 mg/l usually considered high [17,18].

The significant increase in serum CRP concentration in patients with acute HBV infection as compared to healthy control, may be due to the damage of hepatocytes as a result of direct viral replication and indirectly through induction of cytotoxic T cell response that further destroy liver infected cells [19-21].

The results also revealed that the CRP titer 1:16 as a cut-off value provide sensitive and specific predictor for the diagnosis of acute HBV infection when the clinical suspicion was 50%. Unfortunately, no previous studies had been found in the literature regarding the utility of serum CRP concentration in the predictive diagnosis of viral hepatitis. However, our results were consistent with those obtained by utilization of CRP concentration in the predictive diagnosis of other infectious diseases such as community-acquired pneumonia [9,10,22,] and non-infectious diseases such as cardiovascular disease[4-6],diabetes mellitus and hyperlipidemia [7,8].

The significant linear correlation between the CRP concentration and values of liver function tests in patients with acute HBV infection, further candidate the CRP concentration as a surrogate marker in prediction of acute HBV infection beside the clinical picture.

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