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Original Research Article

Role of C-reactive protein in the Assessment of Major Depressive Disorder

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Abstract

Major Depressive Disorder (MDD) is a common psychological problem in the world. In Bangladesh prevalence of MDD is about 4.6%. MDD is associated with reduced quality of life as well as high level of social and occupational impairment. The aim of the study was to investigate the relationship between MDD and inflammation assessed using serum C-reactive protein (CRP). This case control study was conducted at the Department of Laboratory Medicine (Clinical Pathology) in collaboration with the Department of Psychiatry, BSMMU, Dhaka, from March'2016 to February' 2017. A total of 130 patients were enrolled in this study and divided into Group I (cases) and Group II (controls). Each group was consisted of 65 subjects. The patients who fulfilled the criteria of MDD were determined as cases in this study. This study measured C-reactive protein (CRP) in MDD diagnosed patients and healthy controls. CRP was measured by biochemistry auto analyzer (Dimension RxL Max). The mean age was 33.06±12.23 years for patients with MDD and 33.05±11.43 years for the control group. There was no significant difference between the age for groups (p>0.05). Female [43(66.2%)] were predominant in both groups.CRP levels were found to be 5.25±1.84 mg/L in patients with MDD and 2.56±1.16 mg/L in controls. CRP levels were significantly higher in patients with MDD compared to the control group (p<0.05). In ROC analysis, Cut off value of CRP was (>3.58 mg/L) with sensitivity 83.1% and specificity 72.3%. These findings of the study revealed that CRP trend to be higher in MDD. So this marker may be useful tool for assessing MDD.

Keywords: C-reactive protein, Major depressive disorder, psychological problem, quality of life, Laboratory Medicine

INTRODUCTION

MDD is one of the common psychological problems in the world (Baxter AJ et al., 2014). In 2000, depressive disorders were the 4th leading cause of burden as well as of disability in world (Ustun TB et al., 2004). According to World Health Organization (WHO) depressive disorders will be the second leading cause of morbidity worldwide by the year of 2020 (Ebmeier KP et al., 2006). The prevalence of MDD is about 5% worldwide (Ferari AJ et al., 2013). In Bangladesh prevalence of MDD is about 4.6% (Firoz AHM et al., 2007). Male and female ratio is approximately 1:2 (Karim ME et al., 2001). Multiple factors are associated with MDD such as alteration of Central Nervous System (CNS), immune response and vascular reactivity. All of these factors are important in the generation of systemic inflammatory response (Thornton LM et al., 2009). Psychiatric disorders are chronic diseases which are associated with chronic inflammation (Myint et al., 2014). MDD are also

associated with variations in immune responses (Weisse C S, 1992). Some studies showed that inflammatory cytokines in the immune system are associated with the pathogenesis of depression (Fonseka TM et al., 2015, Young JJ et al., 2014). Depression may lead to many organic disorders resulting myocardial infarction, other coronary artery diseases, breathlessness, stroke, diabetes, kidney diseases, arthritis, Parkinson's disease and other autoimmune diseases (Goldberg 2012). C - reactive protein is an acute-phase reactant that synthesized in the liver and secreted in the blood. It has many pathophysiological roles in the inflammatory process. Some pro-inflammatory cytokines are released in MDD (De Berardis D et al., 2009). These cytokines stimulate liver production of acute phase proteins such as CRP (Loucks EB et al., 2006).

MATERIALS AND METHODS

It was a case-control study. This study was conducted at the Department of Laboratory Medicine (Clinical Pathology) in collaboration with the Department of Psychiatry, BSMMU, Dhaka. Study duration was one year (From March 2016 to February 2017). Newly diagnosed all stages of MDD patients without taking antidepressant drugs, attending in the Department of Psychiatry, BSMMU, Dhaka and age, sex matched healthy subjects were enrolled in this study. Control group comprised healthy volunteers who were attendances of patients, attending in the Department of Psychiatry and Laboratory Medicine, BSMMU, Dhaka .

Inclusion criteria

- The patients were included as MDD according to the criteria's of the Diagnostic and Statistical Manual of Mental Disorders (5^{th} edition) and patients were diagnosed by expert psychiatric clinician
- The healthy controls with no previous psychiatric diseases
- Age was ≥18 years old
- Both sexes

Exclusion criteria

The patients were excluded with-
- Anaemia
- Active infections, a leukocyte value suggesting infection
- Other inflammatory or autoimmune diseases
- Severe systemic diseases such as-epilepsy, diabetes mellitus, hypertension, cardiac diseases, hepatic or renal failure
- Alcohol or other substances addiction
- Severe head trauma or mental retardation
- Pregnancy
- Vitamin or fish oil intake
- Heavy smoking (>20 cigarettes/day)
- Obesity (BMI >30 kg/m^2) and concomitant drug use for any reason

Total sample size was 130.
Group I (MDD group):75 patients with MDD were evaluated and 65 newly diagnosed MDD patients were enrolled in this study as cases.
Group II (control group): 65 age sex matched healthy subjects were enrolled in this study as controls.
Consecutive sampling technique was applied for enrollment of the patients in this study. As per inclusion criteria the patients were enrolled in this study. The procedures were explained to the participants and informed written consent was taken.

Specimen collection

About 3.0 ml venous blood was collected from each patient through an aseptic venipuncture from antecubital vein. Blood was collected in plain test tube for CRP measurement.CRP was measured by Biochemistry auto analyzer (Dimension RxL Max) within 2 hours of collection.

Test procedure

CRP was measured by Biochemistry auto analyzer (Dimension RxL Max) using the C-reactive protein extended range (RCRP) method. The RCRP method is based on a particle enhanced turbidimetric immunoassay (PETIA) technique.

Statistical analysis

Statistical package for social science (SPSS) version 23 was used for all statistical analysis. The significance of mean difference between case and control groups were assessed by Student's t test and Chi-square test was used to compare categorical variables. Data were presented as mean ± SD. Receiver operating characteristics (ROC) curve graphics were used in the comparison of sensitivity and specificity. P-value less than 0.05 was regarded as significant.

C-reactive protein

It is a pentraxin family of protein which is generated in the liver and secreted in the blood to play a central role in inflammation. The median CRP concentration is about

Table 1. Age distribution of the study population (n=130)

Age (years)	Study group				p value*
	Case (n=65)		Control (n=65)		
	No.	%	No.	%	
18-25	21	32.3	19	29.2	
25-35	22	33.8	25	38.5	
35-45	11	16.9	14	21.5	
45-55	8	12.3	4	6.2	
55-70	3	4.6	3	4.6	
Mean ± SD	33.06 ± 12.23		33.05 ± 11.43		0.994^{ns}

*t test was done to measure the level of significant. ns = not significant

Table 2. Sex distribution of the study population (n=130)

Sex	Study group				p value*
	Case (n=65)		Control (n=65)		
	No.	%	No.	%	
Male	22	33.8	22	33.8	0.999^{ns}
Female	43	66.2	43	66.2	

*Chi-square test was done to measure the level of significant. ns = not significant

Table 3. Laboratory test results of mean difference between cases and controls (n=130)

Parameters	Study group		p value*
	Case (n=65)	Control (n=65)	
	Mean ± SD (Min-max)	Mean ± SD (Min-max)	
CRP(mg/L)	5.25 ± 1.84 (1.98-10.20)	2.56 ± 1.16 (0.34-4.40)	0.001^{s}

*t test was done to measure the level of significance. s= significant

1 mg/L and 99th percentile is about 10 mg/L in plasma of normal individuals (Bock JL et al., 2007). Normal reference value of CRP is <5mg/L. Mean CRP levels were 4.4±8.4mg/L in MDD group (Sawyer J., 2016).

Ethical consideration

Prior to the commencement of this study, the research protocol was approved by the Ethical Institutional Review Board (IRB) of BSMMU, Dhaka.

RESULTS

Table 1 shows distribution of the respondents by age (n=130). Age group, 18-25 years 21(32.3%) were in cases and 19(29.2%) in control group. Age group, 25-35years 22 (33.8%) were in cases and 25(38.5%) in control group. Age group, 35-45 years 11(16.9%) were in cases and 14(21.5%) in control group. Age group, 45-55years 8 (12.3%) were in cases and 4(6.2%) in control group and age group, 55-70 years 3(4.6%) were in cases and 3(4.6%) in control group. The mean age was found 33.06±12.23 years in cases and 33.05±11.43 years in controls. Among the five age groups first 3 groups (18–45) show majority of patients in cases and controls. Student's t test showed that the mean age of two groups of population were similar with no significant difference (p>0.05).

Table 2 shows distribution of the respondents by sex (n=130). Female were predominant in both groups. Female were 43(66.2%) in cases and controls. Male were 22(33.8%) in both groups. Similar numbers of male and female were in two groups. Difference was not statistically significant between the two groups (p>0.05).

Table 3 shows mean CRP were 5.25±1.84mg/L in cases and 2.56±1.16mg/L in control group (p<0.05).

Table 4. Distribution of the study population according to groups with CRP (n=130)

CRP (mg/L)	Case (n=65)		Control (n=65)		p value*
	n	%	n	%	
Raised (>3.58)	54	83.1	18	27.7	0.001[s]
Normal	11	16.9	47	72.3	
Total	**65**	**100**	**65**	**100**	

*Chi-square test was done to measure the level of significance.s= significant

Table 5. Validity of diagnostic tests

Diagnostic tests	Sensitivity	Specificity	PPV	NPV	Accuracy
CRP(mg/L)	83.1%	72.3%	75.0%	81.0%	77.7%

PPV = Positive Predictive Value
NPV = Negative Predictive Value

Values (mean±SD) were expressed in between groups and analysis was done by Student's t test (un paired).

Table 4 shows distribution of the study population according to groups with CRP (n=130). Raised (>3.58 mg/L) CRP was found in 54(83.10%) with cases and normal CRP was found in 18(27.7%) with MDD patients. Raised (>3.58 mg/L) CRP was found in 11(16.9%) with control group and normal CRP was found in 47(72.3%) with control group. The difference was statistically significant between two groups ($p<0.05$).

Table 5 shows that sensitivity of CRP was 83.1%, specificity 72.3% accuracy 77.7%, positive and negative predictive values were 75.0% and 81.0% respectively.

DISCUSSION

This study demonstrated that mean CRP level was 5.25±1.84 mg/L in patients with MDD group and mean CRP level was 2.56±1.16 mg/L in the control group. CRP levels were significantly higher in depression group relative to controls ($p <0.001$). The present study is comparable with several studies that have reported a positive association between CRP and depression (Sawyer J., 2016, Jangpangi D et al., 2014, Penninx B W et al., 2003, Berk M et al., 1997, Sluzewska A et al., 1996). Sawyer J., (2016) showed mean CRP levels were significantly higher in the depressed population than in the healthy control group (4.4±8.4mg/L vs. 1.6±2.0mg/L)($p<0.05$). Jangpangi D et al., (2014) also found that the serum levels of hsCRP (ng/ml) were significantly higher in depression group as compared to the control group (2132±50.24 vs 1969±69) ($p<0.05$). Most of the studies have found an association between depression and inflammation, other studies have not consistently obtained the same results. (Kagaya A et al., 2001). So, it can be said that pathophysiology of depression is uncertain and is possibly varied and complex. Inflammation may play an indirect role or may act as a risk factor ultimately leading to depression in susceptible individuals (Krishnadas R et al., 2012). The study examined inflammatory markers in clinically diagnosed depressive patients prior to initiation of therapy. This study also excluded subjects with other psychiatric and physical co-morbidities that could potentially confound the results. However, there are some limitations in our study, one is small sample size. Longitudinal studies are required to examine whether inflammation precede the depression or followed by depression or whether there is a bidirectional relationship (Stewart JC etal., 2009).

CONCLUSION

Our study showed that CRP were found higher impatience with MDD than healthy controls. So this parameter can be used as a valuable and effective tool for the management of MDD and treatment follow up.

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