Investigation of the Relationship between Inflammatory Factors CRP, IL-6 and IL-1â and Major Depressive Disorder: A Hospital Based,Case-Control Study

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Abstract

Objective: The present study aims to investigate the relationship of these factors and major depressive disorder in a sample of patients presenting to the psychiatry department of the teaching hospital of a private medical college in Islamabad, Pakistan.

Methods: Using convenience sampling a total of 50 participants were included in the study which comprised of 25 patients with major depressive disorder (MDD) and 25 matched healthy controls (HC). The severity of depression was determined with the help of Hamilton Rating Scale for Depression (HRSD) while the demographic details of the participants were collected with the help of a proforma. The pro-inflammatory markers (CRP, IL-6 and IL-1â) were measured in the serum by taking peripheral venous samples from both cases and controls. Statistical analysis was performed by using SPSS, version 22.

Results: Patients with MDD had significantly higher levels of the proinflammatory factors as compared to healthy controls. In HC the levels of proinflammatory cytokines were not raised to any significant degree, while these were consistently higher in MDD patients with acute depressive episodes (two sample *t* test 2-tailed significance d" 0.01).

Conclusion: This study showed that sensitive indicators of inflammation were higher in the local patients with MDD. Our study lends support to the inflammatory hypothesis of major depression, so that there is a further need to investigate this avenue. In this manner it would be possible to discover much needed biomarkers, while opening new paths to more effective therapeutics of this recalcitrant disorder.

Keywords: C-reactive protein, cytokines, inflammation, major depressive disorder

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Introduction

Major depressive disorder (MDD) is a severe mental disease with a life-time prevalence of approximately 20%[1]. World Health Organization considers MDD among top ten diseases causing disability and premature daeth[2]. Characterized by episodes or exacerbations, in MDD the patients experience low mood which is the sine qua non of this illness. In addition, there are other symptoms such as loss of pleasure in day to day activities, excessive guilt, decreased sleep and appetite, diminished energy levels and ominously, suicidal ideation. The illness is episodic in nature but often symptoms persist in the inter-episode period, such that the sufferers continue to experience difficulties in the biological, psychological and social domains of functioning[3]. Principal mood disorders are classified into major depressive disorder and bipolar disorder; the former is epitomized as unipolar depression whereas the latter is characterized by both manic and depressive episodes[4].

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Major depressive disorder is a chronic condition and causes severe psychological and physical symptoms. MDD has a pervasive negative effect on health and well-being, such that there is an urgent need to find quick and lasting cures. Modern conceptualization regards MDD as not just a disease of brain but a multi-organ disorder which impacts all systems of the body[5]. Metabolic abnormalities manifesting as glucose intolerance, dyslipidemia, and atherosclerotic disease cause increased cardiovascular morbidity and premature mortality in these subjects[6]. In order to explain the pervasive nature of MDD the inflammatory hypothesis has been put forward which suggests that there is a persistent low grade inflammatory state in the body responsible for both the central and peripheral manifestations of this condition[7].

Research is directed at finding new treatments which act as lasting cures for this intractable disorder. In the past couple of decades mounting evidence has incriminated central and peripheral inflammatory factors in the etiology and pathogenesis of mood disorders[8]. It is hypothesized that during acute exacerbations of MDD there is neuroinflammation which has a deleterious effect on brain functions via dysfunction in key neurotransmitters[9]. Ideally, sensitive indicators of inflammation detectable through the examination of peripheral blood serve as biomarkers of MDD[10]. Cytokines are small proteins released by immune cells and present in the blood in minute amounts (picograms per milliliter- pg/ml), detectable by special techniques such indirect sandwich ELISA[11]. In major depressive disorder, during acute episodes there is a rise in CRP, pro-inflammatory cytokines and chemokines and a decrease in anti-inflammatory cytokines[12]. With successful treatment these abnormalities are reversed to a significant extent, and during euthymic periods inflammatory factors may return to normal[13].

While a vast literature exists on the subject of inflammation and MDD, there is woefully little research effort from the perspective of the local population[14]. With this background, our study intended to investigate key inflammatory markers in MDD subjects presenting as outpatients. We recruited consecutive patients with major depressive episodes (MDE), either index episodes or relapses with or without psychotropic medications and measured levels of CRP, interleukins IL-6 and IL-1â in the peripheral blood. We enlisted matched healthy controls without psychiatric history and measured these same factors to compare the two samples. The aim of the study was to examine whether there was an association of inflammatory factors i.e. CRP, IL-6 and IL-1â and acute episodes of MDD as compared to HC.

Methodology

This was an observational, case-control study conducted from 01/05/2023 to 31/10/2023 for a period of 6 months at the Outpatients unit of the Department of Psychiatry, HBS General Hospital, a tertiary care teaching hospital of HBS Medical & dental College, Islamabad. The study protocol was approved by the Ethical Review Board of the medical college.

In the study non-probability, convenience sampling technique was utilized and consecutive patients presenting with MDD were enrolled after obtaining written consent. Patients, both males and females, aged between 18 to 65 years were included in the study if they were suffering from a DSM-5 defined major depressive episode as determined by history and mental state examination. Hamilton Rating Scale for Depression (HRSD) was instituted to all MDD patients to determine the severity of depression. Patients were excluded if they concomitantly suffered from chronic inflammatory conditions (e.g. rheumatoid arthritis, systemic lupus erythematosus, etc), acute infections, and systemic disorders (diabetes mellitus, uncontrolled hypertension, and metabolic syndrome). Similarly, patients on long-term treatment with non-steroidal anti-inflammatory analgesics were excluded, and lastly pregnant females were also not enrolled in the study. In this manner 25 MDD cases were selected and a control group consisting of 25 healthy adults with no previous psychiatric history was also recruited. A semi-structured proforma with demographic details was administered to all participants.

for sample size calculation the following formula was used:

$$\text{Unlimited population: } n = \frac{z^2 \times \hat{p}(1-\hat{p})}{\varepsilon^2}$$

$$\text{Finite population: } n' = \frac{n}{1+\frac{z^2 \times \hat{p}(1-\hat{p})}{\varepsilon^2 N}}$$

Where **z** is the z score, **å** is the margin of error, **N** is the population size, and **p** is the population proportion.

By using confidence interval of 85% and margin of error of 15% a sample size of 24 was derived and applied for the purpose of the study. After following the necessary precautions for phlebotomy, venipuncture was performed and 5 ml of blood was collected from each participant. Serum was separated by centrifugation and biochemical analysis was done on the following biomarkers: IL-1â, IL-6 and CRP.

Serum IL-1â and IL-6 were analyzed using human sandwich enzyme-linked immunosorbent assay (ELISA) kits and the detection range for both cytokines was from 7.81 to 500 pg/ml, whereas CRP was analyzed by Avitex-CRP latex particles coated with antibodies to human CRP.

Analysis was performed by Statistical Package for Social Sciences (SPSS) Version 22, copyright IBM Corporation, Armonk, NY, USA, 2013. The inferential analysis was performed by using the two-sample *t*-test, a calculator which exactly measured the difference between two means. Its focus was on the same numeric data variable rather than counts or correlations between multiple variables and was particularly useful for small samples of less than 30 observations. The two means compared in this study were the control group and the MDD group. The analysis was performed by using the two-sample t test, comparing the two datasets to see if their means were statistically different. For the purpose of our calculation we employed the most general formula for a *t* test which was composed of two means (M1 and M2) and the overall standard error (SE) of the two samples, calculated with the help of SPSS: $t = M_1 - M_2 / SE$

Results

Table 1 used descriptive statistics applied on demographic variables. For continuous variables like age, mean and standard deviation were calculated, while for categorical variables such as gender and marital status frequency and percentage were computed. The mean and standard deviation for HRSD scores for the MDD group was also determined. It could be seen that the control and MDD groups were largely comparable across different demographic variables. Moreover, the mean HRSD score of the MDD group was in the moderate to severe range (26.96 ± 5.59) which implied that the depressed sample had an overall greater burden of depressive symptoms. As the control group was by definition free of psychological symptoms, HRSD was not applied and no further statistical analysis was performed in this regard.

Table 2 provided inferential analysis of the data and means of the inflammatory markers of the MDD and control groups were compared using the two sample *t*- test. The significance level was *p* d" 0.01 and the results showed that the inflammatory factors i.e. CRP, IL-1â and IL-6 were significantly elevated in the MDD group compared to healthy controls. This provided unequivocal evidence that sensitive markers of inflammation were higher in patients with major depressive episode. Since major depression reflected grave perturbation in brain functioning, increased inflammatory factors in the patients served as biomarkers of the disease state. Furthermore, replication of this study's results in larger, prospective cohorts could identify the inflammatory factors as indicators of this diathesis which would be useful in the clinical setting.

Table 1. Demographic characteristics of the study participants

Variable	Group	n	Mean ± SD
Age (years)	Total MDD	50	37.80 ± 8.10
	group controls	25	33.72 ± 8.93
		25	
HRSD score	Total	50	26.96 ± 5.5900
	MDD group	25	
	Healthy controls	25	
Gender	**Total**	50	Percentage %
	MDD group		
	Male	11	44.0
	Female	14	56.0
	Healthy controls		
	Male	15	60
	Female	10	40
Marital status	**Total**	50	
	MDD group		
	Married	16	64
	Single	09	36
	Healthy controls		
	Married	14	56

HRSD – Hamilton Rating Scale for Depression; MDD – Major Depressive Disorder; SD – standard deviation

Table 2. Comparison of inflammatory markers of MDD and control groups by two sample *t*-test

	MDD cases					
	t	df	Sig. (2-tailed)	Mean difference	95% CI of the difference Lower	Upper
CRP level	6.363	24	0.000	3.04000	2.0539	4.0261
IL-1â level	2.818	24	0.001	0.730160	0.19547	1.26485
IL-6 level	8.651	24	0.000	9.957680	7.58213	12.33323
	Healthy controls					
	t	df	Sig. (2-tailed)	Mean difference	95% CI of the difference Lower	Upper
CRP levels	Standard deviation is 0 so results cannot be computed					
IL-1â	2.391	24	0.025	0.421200	0.05768	0.78472
IL-6	1.553	24	0.134	0.317280	- 0.10438	0.73894

CI – Confidence Interval; MDD – Major Depressive Disorder

Discussion

Our study clearly shows that sensitive markers of inflammation are significantly increased in the peripheral blood of patients suffering from MDD. In the next few paragraphs the relationship between inflammation and major depression is elucidated in order to illuminate the findings of our study.

As a context, MDD is a prevalent condition affecting both males and females of all age groups, but the main sufferers are young adults and middle aged individuals. It may be acute and episodic, but can also assume a chronic state wherein the functioning of the sufferers is adversely effected for prolonged periods of months and years[15]. Parallel res-

earch findings in humans and animal models of depression incriminate inflammatory factors in this multi-faceted disorder. Emerging evidence indicates that inflammation involves the brain which is defined by the term “neuroinflammation”. This hypothesis posits that inflammatory factors affect brain functioning principally through dysregulated neurotransmission and lead to myriad signs and symptoms of depression[16].

An Increasing body of research points to the possible role of the inflammatory response in the pathogenesis of major depressive disorder. In this regard a number of original studies and meta-analyses have demonstrated an increase in systemic inflammatory factors in subjects with MDD. To extend this argument further, modern sedentary life style factors may contribute to chronic systemic inflammation. Peripheral pro-inflammatory cytokines reach the brain by crossing the blood-brain barrier and contribute to neuroinflammation by activating cellular, humoral and neural pathways. From the perspective of therapy, psychotropic medications acting through diverse psychodynamic mechanisms evidently decrease the neuroinflammation. This is manifested as an improvement in the clinical state and relief from the manifold symptoms of depression. Furthermore, anti-inflammatory drugs such as NSAIDs, lifestyle modification and nutritional alterations also lessen inflammation and manifestly improve the depressive symptoms[17]. The rationale of these therapeutic approaches is that reduced burden of inflammation provides relief from the multifarious psychological and physical symptoms of MDD. The purpose of providing this background is to illustrate the overarching role of inflammation in the pathogenesis and management of MDD, which is a recalcitrant condition.

In this paper subtle indices of inflammation are elevated in the peripheral plasma of MDD patients as compared to healthy controls. So how do inflammatory molecules lead to deranged functioning of the brain? In this regard, recent evidence shows that raised inflammatory factors in the peripheral blood can serve as biomarkers of neuroinflammation, while also triggering the microglia which are the resident macrophages in the brain. The latter is exemplified as a state in which microglial cells in the brain are stimulated by inflammatory molecules. The activated microglia amplify the inflammatory response in the brain resulting in diminished secretion of neurotrophic factors, activation of pro-apoptotic pathways and inhibition of neurogenesis in the hippocampus. Our original study was conducted in the local population to investigate this supposed relationship and appeared to validate the inflammatory hypothesis of MDD. We examined CRP and IL-6 and IL-1â levels in the serum of patients with MDD having an acute episode and compared them with healthy controls. Our results showed that all factors mentioned above were significantly elevated in cases as compared to controls (Table 2).

To elucidate the role of IL-6, a recently published study examined the relationship between IL-6 and treatment of MDD with sigma-1 receptor modulator fluvoxamine. The study showed that in patients with high levels of inflammation as evidenced by increased serum IL-6 levels, fluvoxamine treatment lead to remission of symptoms along with reductions in IL-6 levels [18]. Thus it can be assumed that the pro-inflammatory cytokine, IL-6 is an important mediator of depression.

A meta-analysis of case-control studies was published investigating the role of IL-1â in MDD. Results showed that in high quality studies only, there was an association between increased plasma IL-1â and MDD[19]. In the meta-analysis qualitative examination of the data indicated that MDD coupled to a history of childhood trauma may be a subgroup for IL-1â targeted therapies as this biomarker was elevated in the subgroup. This interesting study showed the value of IL-1â as a promising biomarker for fresh treatment perspectives in MDD. Therefore, as shown in our study, raised IL-1â is a key biomarker of MDD and further research is needed before it can be applied in clinical practice.

An open label trial examined serum pro-inflammatory cytokine and chemokine levels in monitoring response to the first line SSRI, escitalopram. It showed that high levels of inflammatory factors in

the blood were associated with poor response to the medication. Moreover, increased levels of inflammatory factors in these cases lead to a diminished response to the combined treatment regimen of escitalopram plus adjunctive aripiprazole[20]. So, there may be a sub-class of depression with raised inflammatory factors which is more severe and resistant to therapy with first-line antidepressant medications.

Major depressive disorder can be severe in which biological interventions like pharmacotherapy and electroconvulsive therapy are required, whereas in mild to moderate depression psychotherapy alone is beneficial. A recently published study with a randomized controlled design from the People's Republic of China compared two groups of college students suffering from MDD. One group was provided active treatment for 8 weeks in the form of mindfulness based cognitive therapy, while the other group with MDD was placed on waiting list which meant no active therapy. All the study participants were administered Patient Health Questionnaire, Generalized Anxiety Disorder Scale, and Pittsburgh Sleep Quality Index at inception of the study, repeated at week 4 and finally at week 8. Also, the serum levels of IL-1â, IL-6, IL-8, TNF-á, BDNF were measured at baseline and post-intervention. It was discovered that in the intervention group there was a significant reduction in the scores of the psychometric instruments as compared to the waiting list group who had received no therapy. Interestingly the levels of pro-inflammatory factors declined significantly in the former group compared to the latter, while BDNF levels showed an increase in the cases who had received active therapy[21]. This study demonstrated that MDD had an inflammatory component and active treatment in the form of psychotherapy exerted a therapeutic effect which was quantifiable by measuring sensitive peripheral blood indices. In the context of our study this research further strengthens the role of inflammatory factors in the pathogenesis and treatment of a severe mental disorder.

Discovery of biomarkers in MDD aids in diagnosis, as well as being helpful in realizing the aim of better and more effective therapeutics. In this regard, an interesting paper was recently published by Chinese investigators who simultaneously studied human subjects with MDD and murine model of depression via intraperitoneal injection of lipopolysaccharide (LPS). Moderate to severe depressive disorder patients were enrolled and the serum concentrations of IL-6 and TNF-á were measured. The correlation of these cytokines with the Hamilton Depression Rating Scale (HRSD-24) scores was evaluated, and their role in distinguishing MDD patients from health controls was assessed. A depression rat model was meanwhile established by giving intraperitoneal injection of LPS and tocilizumab (IL-6 antagonist) was administrated via intravenous injection. In the animals the behavioral performance was observed, the serum concentrations of IL-6, TNF-á, and C-reactive protein were measured, and the protein expression of IL-6 and TNF-á in the hippocampus was also detected. The results showed that the serum IL-6 level was significantly increased in the patients and LPS-challenged rats, with a significant correlation with the HRSD scores or struggling time in the tail suspension test. Results of ROC (receiver operator curve) analysis disclosed a significant diagnostic value of IL-6 in discerning MDD patients or depression rats from the controls. In the tested animals tocilizumab relieved the depression-like behaviors induced by LPS; moreover, the medication alleviated the inflammatory storm and improved the impaired hippocampal synaptic plasticity in the LPS-challenged depression rats. There was inhibition of the triggered astrocytes and microglia and decrease in the peripheral and central abundance of IL-6, CRP, and TNF-á. Furthermore, in these same animals there was balancing of the hippocampal expression levels of synaptic plasticity-associated proteins and key molecules in Wnt/â-catenin signaling pathway. These results showed an extrapolative value of IL-6 in clinically distinguishing depressed patients from controls. It was demonstrated that an antidepressant effect of tocilizumab occurred in the LPS-challenged rats which appeared to target the inflammatory storm and the subsequent impairment of hippocampal synaptic plasticity[22]. The significance with respect to our study lays in the fact

that same inflammatory factors are incriminated and further research can lead to the discovery of new avenues of treatment.

Suicidal ideation is the most serious manifestation of MDD, as this is the common underlying factor in most victims of suicide. A recent study scrutinized patients with suicidal ideation, utilizing structural MRI of the brain and serum IL-6 levels. The study showed decreased gray matter volumes in critical mood regulating areas of the brain, but this finding was negatively correlated with serum IL-6 levels. These results provided new insights into the pathophysiological mechanisms of MDD patients who also had suicidal ideation and strengthened the neuroinflammatory hypothesis of depression[23]. Indeed, as demonstrated in our study elevated IL-6 signifies a more severe form of depression and serves as a key marker of patients at risk for suicide.

A revealing meta-analysis was recently published which investigated inflammatory factors (CRP, IL-1â, IL-6 and TNF-á) in patients who had suicidal ideation or committed acts of self-harm. Data was based on 36 studies including 2679 persons with suicidal behaviors and 6839 comparison subjects who had a psychiatric illness but did not show such behavior. The inflammatory markers were significantly increased in cases versus the comparison group; moreover, meta-regression and subgroup analyses revealed that increased serum CRP in acts of self-harm was mainly determined by recent suicidal behavior. This data associated the immune system and inflammatory response in suicidal behavior independent of a relationship to major psychiatric disorders. Furthermore, the measured biological factors were mainly state-dependent markers associated with suicidal behavior[24]. Hence, as research evidence mounts it becomes evident that incorporation of sensitive indices of inflammation is a necessary pre-requisite in the assessment of any serious psychiatric patient regardless of diagnosis.

Finally, an interesting study sub-grouped patients with refractory depression into inflamed and non-inflamed sub-categories utilizing high sensitivity CRP cut-off value of 3 mg/L. The investigators measured serum proinflammatory cytokines and vitamin D levels in the study subjects. The inflamed subgroup (hs-CRP > 3) exhibited significantly higher BMI, higher cytokines and greater IL6-IL8/Vit D ratios than the noninflamed group (hs-CRP d" 3). These findings supported the premise that in patients with major depression there was an inflamed subgroup who had distinguishing biological and clinical features and could therefore be targeted with anti-inflammatory treatments adjunctive to first line antidepressant medications [25]. Indeed, C-reactive protein can be utilized in severely depressed patients for the purpose of sub-classification and directed precision therapy for improved outcomes.

The limitations of the study lie in the sample size that is small and in order to replicate the findings, studies with larger number of participants are required. Also, the design is cross-sectional; prospective, cohort studies can better confirm or refute the results presented here. Serum cytokine levels are sensitive indicators of an inflammatory state, but these are not performed routinely and there are technical and financial barriers in conducting such studies.

Conclusion

Major depressive disorder is a challenging condition to diagnose and manage. There is an urgent need to discover reliable biomarkers which can be replicated and used in clinical practice. A very large number of patients show poor response to currently available antidepressant medications. Inflammatory factors in the peripheral blood are being investigated as markers of severity and treatment response in MDD, and in this regard an increasing body of evidence is supportive of the inflammatory hypothesis. This study was conducted in the local population and the results are in line with international studies. Our study further strengthens the supposition that inflammatory factors play a pathophysiological role in MDD. It is hoped that further research will be instrumental in the diagnosis, sub-.

classification and monitoring of the treatment response in MDD which is an intractable neuropsychiatric condition.

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