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Original Research Article

A Study of Association of Elevated CRP in Depression

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Abstract:

Introduction: Depression is associated with increased serum C- reactive protein levels in circulation. Major depressive disorder manifest all of the cardinal features of an inflammatory response. Increase in inflammatory cytokines causes reduction of serotonin and other neurotransmitters in CNS and increases the activation of hypothalamic pituitary adrenal axis, leading to elevated oxidative stress in the brain. The levels of CRP may differ depending on the severity of depression.

Aim and Objective: To study the association between depression and CRP levels according to the severity.

Materials and Methods: A cross sectional study was conducted in Psychiatry Department, in patients presenting with major depressive disorder from May 2023 to October 2023, in tertiary care hospital of Surendranagar district. The patients were assessed by thorough history taking and fulfilling the DSM 5 criteria for Major Depressive Disorder. Total 45 patients fully met the criteria, and further assessment for severity of depression was done. Serum CRP levels were also assessed.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by " The Institutional Ethics Committee and Scientific Review Committee - Subcommittee (Human Research) of C. U. Shah Medical College, Surendranagar and approval number CUSMC/IEC(HR)/Pro.Approval-RP-05/2023/OUT- 41/2023.

Results: A Kruskal Wallis H test showed that there was a statistically significant difference in CRP levels between the different groups of depressive patients according to the severity. Kruskal Wallis H= 8.520, p=0.025, with a mean CRP score of 18.17 for mild , 26.53 for moderate and 33.20 for severe depression.

Conclusion: It can be concluded that there is significant association of serum CRP levels with severity of depression. Also depression can be correlated with gender, socioeconomic status and marital status.

Keywords: Depression, inflammation, C- reactive protein.

Introduction

Depression is one of the most common psychiatric illness with a point prevalence of around 12.9%. [1, 6] Today, depression is already the second cause of DALYs in the age category of 15-44 years. [2] Depression is also associated with high suicidality, about 50% of individuals who have committed suicide carried a primary diagnosis of depression. A significant percentage of people committing suicide are below 30 years of age. [3] It is also highly associated with significant risk if cardiovascular morbidity and mortality.

Depression has an elevated risk of recurrence and chronicity. The rate of depression in patients with cardiovascular disease ranges between 20-40% [4] The increased levels of proinflammatory cytokines are associated with development of major depressive disorder. Increase in inflammatory cytokines causes reduction of serotonin and other neurotransmitters in central nervous system (CNS) and further reduces the activation of hypothalamo-pituitary-adrenal axis, leading to elevated oxidative stress in the brain. This increased oxidative stress leads to increased cardiovascular morbidity and mortality, including hypertension, stroke, myocardial infarction and congestive heart failure. [5] The objective of the present study is to find out the levels of circulating CRP in serum and its association with severity of depression according to Beck's depression Inventory scale.

Aim of the Study: To study the association between depression and CRP levels according to the severity of depression in a tertiary care hospital.

Materials and Methods

It was a cross sectional, observational study, in 45 drug naive, newly diagnosed patients according to DSM -5 criteria for Major Depressive Disorder suffering from depression. Patients were from outpatient as well as indoor patients of Department of Psychiatry, C. U. Shah Medical College and Hospital, Surendranagar, Gujarat. Time period for conducting the study was 6 months from May 2023 to October 2023.

Sample collection was done on the basis of convenient sampling, after explaining and taking consent from patients. For assessing severity of depression, Beck's Depression Inventory scale (BDI 2) was used in all patients through a structured interview. Levels of CRP were also assessed. Written informed consent was obtained from all patients. Approval was granted from Ethics committee of C. U. Shah Medical College, Surendranagar. The funding of investigation (CRP) was supported by C. U. Shah medical college and hospital.

Inclusion Criteria: Patients of all ages of either sex fulfilling the DSM 5 criteria for diagnosis of Major Depressive Disorder were included in the study.

Exclusion Criteria: Patients with history of any metabolic syndrome and cardiovascular disease or history of smoking were excluded.

Sample Size: 45 patients

Diagnosis and Statistical Analysis

The diagnosis of Major Depressive Disorder was done by DSM 5 criteria and BDI 2 scale was applied for severity of depression.

DSM-5 criteria for diagnosis of major depressive disorder:-

A) Five or more of the following symptoms present during 2 week period and represent a change from previous functioning is either
1) Depressed mood
2) Loss of interest or pleasure
1) Depressed mood most of the day, nearly every day, as indicated by subjective report or observation made by others.
2) Markedly diminished interest or pleasure in all, or almost all activities most of the day, nearly everyday.
3) Significant weight loss or weight gain or decrease or increase in appetite nearly everyday.
4) Insomnia or hypersomnia nearly everday
5) Psychomotor agitation or retardation nearly everyday.
6) Fatigue or loss of energy nearly everyday
7) Feelings of worthlessness, excessive or inappropriate guilt nearly everyday
8) Diminished ability to think or concentrate or indecisiveness, nearly everyday.
9) Recurrent thoughts of death, recurrent suicidal ideation without specific plan or suicide attempt or specific plan for committing suicide.

B) The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

C) The episode is not attributable to physiological effects of substance or to another medical condition.

D) The occurrence of episode is not better explained by schizoaffective, schizophrenia or schizophreniform, delusional disorder or other specified and unspecified psychotic disorders.

E) There has never been a manic or hypomanic episode.

Severity of depression was done after diagnosing, by applying BDI (Beck's depression inventory-2) scale.

SEVERITY	BDI 2 SCORE
Minimal	0-13
Mild	14-19
Moderate	20- 28
Severe	29-63

The levels of CRP < 5 mg/L were considered normal.

Statistical analysis was done.

Comparison of serum CRP levels with severity of depression was done using Kruskal- Wallis H test.

Data analysis: Data were entered and analysed using Microsoft excel version 2021.

Results

A total of 45 patients (13 female and 32 male) were taken, from which 23 had mild depression, 17 had moderate and 5 had severe depression according to BDI 2 scale.

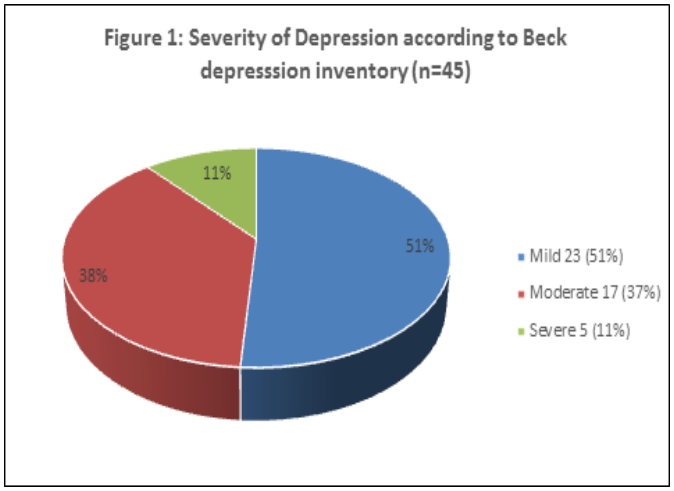

Table 1: Sociodemographic characteristics of depressive patients and their association with depression

Sociodemographic Factors	Mild n(%)	Moderate n(%)	Severe n(%)	Grand Total(n=45) n(%)
Gender				
Female	6(26%)	6(35%)	1(20%)	13(29%)
Male	17(74%)	11(65%)	4(20%)	32(71%)
Religion				
Hindu	20(87%)	13(76%)	5(100%)	38(84%)
Muslim	3(13%)	4(24%)	0	7(16%)
Socioeconomic status				
Lower	19(83%)	11(65%)	2(40%)	32(71%)
Middle	4(17%)	6(35%)	3(60%)	13(29%)
Marital status				
Married	14(61%)	12(71%)	3(60%)	29(64%)
Unmarried	6(26%)	1(5%)	0	7(16%)
Widow	3(13%)	4(24%)	2(40%)	9(20%)

Here, Table 1 depicts association of the severity of depression with different sociodemographic factors. Overall, depression is seen more in male gender, following hindu religion, belonging to lower socioeconomic status.

Normality testing

Table 2

Tests of Normality							
	Depression coding	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
CRP	mild	0.251	23	0.001	0.823	23	0.001
	moderate	0.261	17	0.003	0.837	17	0.007
	severe	0.246	5	0.200*	0.895	5	0.385

Not following normal distribution so Kruskal-Wallis H test

Table 3: Kruskal-Wallis H test for difference in CRP level based on depression severity

Depression Group	N	Mean Rank	Kruskal-Wallis H	df	Asymp. Sig.
Mild	23	18.17	7.349	2	0.025
Moderate	17	26.53			
Severe	5	33.20			
Total	45				

A Kruskal-Wallis H test showed that there was a statistically significant difference in CRP Level between the different Depressive group, Kruskal-Wallis H = 8.520, p = 0.025, with a mean rank CRP score of 18.17 for Mild depression, 26.53 for Moderate depression and 33.20 for Severe depression.

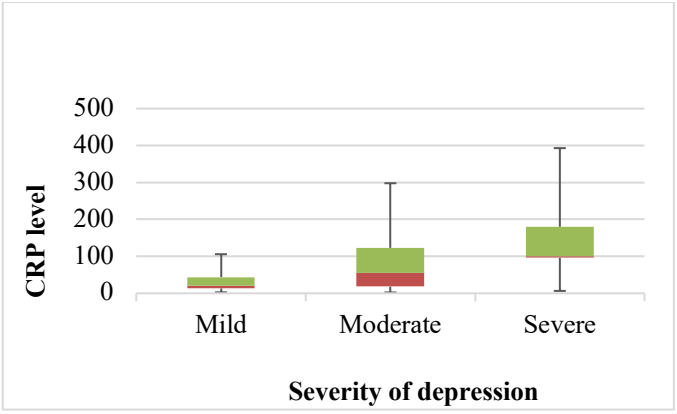

Figure 2: depicts severity of depression with CRP level. Box and whisper plot showing that mild depressive patient having median CRP level 21.34 and interquartile range 30.75. Moderate depressive patient having median CRP level of 55.75 with interquartile range 105. Severe depressive patient having median CRP level of 100.2 with interquartile range 84.2.

Dispersion in CRP level was found more in moderate category followed by severe and mild.

Discussion

It is known that in depression the levels of serotonin decreases in synapses, and so the antidepressants which increases the levels of serotonin play an important role in the major depressive disorder. Also the CSF levels of serotonin decreases. Serotonin is synthesized from the amino acid Tryptophan. [6]

Tryptophan is an important amino acid in depression. It is metabolized in two important pathways: the serotonin and kynurenin pathways. The maintenance of balance of serotonin and kynurenin pathways is critical for human physiological homeostasis. [8]

Studies demonstrates that depressive-like behaviour was the result of metabolic end products of the tryptophan–kynurenine pathway. Of these end products, quinolinic acid and 3-hydroxykynurenine caused anxiety and stress-like changes, thereby suggesting that there was a neurochemical link between anxiety and depression.

There has been a renewed interest in the tryptophan–kynurenine pathway which has been stimulated by the reduction in brain serotonin and plasma free tryptophan, and an increase in the metabolites of kynurenine in the blood and CSF in major depression [9].

Under non-stress conditions tryptophan is primarily metabolised in the liver to kynurenine by tryptophan 2,3-dioxygenase under the influence of circulating glucocorticoids. However, in stressful and inflammatory conditions tryptophan is metabolised by indoleamine 2,3-dioxygenase (IDO) which is widely distributed in immune cells, lung, kidney and the brain. Anti-inflammatory cytokines reduce the activity of IDO. There is also evidence that some proinflammatory cytokines such

as IL-1β reduce hippocampal neurogenesis. [10]

Approximately 60% of brain kynurenine arises from the blood where it is further metabolised to either the excitotoxic metabolite quinolinic acid, which acts as an agonist at NMDA glutamate receptors. Neuroprotective metabolite kynurenic acid acts as an antagonist at the NMDA receptor. [11] Under non inflammatory/non-stress conditions there is a balance between the end products of the neurodegenerative and neuroprotective pathways. [12] The distribution of the tryptophan–kynurenine pathway in the brain is concentrated mainly in the astrocytes and microglia. In the astrocytes, kynurenine is mainly synthesised to kynurenic acid by kynurenine aminotransferase whereas in the microglia it is primarily converted to 3-hydroxykynurenine and quinolinic acid. Under non-inflammatory conditions the end product of kynurenine metabolism is kynurenic acid but following the activation of the microglia by stress or inflammation the neurodegenerative pathway predominates. This results in the exposure of neurons to the exotoxic kynurenine metabolites thereby contributing to the decrease in the brain volume reported to occur in patients with chronic schizophrenia or depression. [13]

Thus as a consequence of immune activation the changes in the tryptophan–kynurenine pathway play a major role in the dysfunctional neurotransmitter systems in the brain and, contribute to the changes in the brain structure and function which characterize depression. In recent years, attention has centred on the neurotoxic consequences of the increase in quinolinic acid and the intermediates formed from kynurenine in the tryptophan–kynurenine pathway.

The monoamine hypothesis of depression, that has formed the basis for an understanding of the

psychopathology of depression has concentrated attention on dysfunction of the serotonergic, noradrenergic and dopaminergic systems and the role of neuropeptides, such as corticotropin releasing factor and BDNF. A dysfunctional immune and endocrine system play an increasingly important role in major psychiatric disorders. [14]

Antidepressants increase the intracellular concentration of cyclic adenosine monophosphate (cAMP) by activating the G-protein coupled monoamine receptors and also by reducing the activity of intraneuronal phosphodiesterase which catalyses cAMP. [15,16] A consequence of physical or psychological stress in those predisposed to depression is the activation of the inflammatory pathways. Thus if the pathological changes in depression are attributable to an impairment of neuronal structure and function, it can be hypothesised that anti-inflammatory drugs, and drugs that inhibit the synthesis of NO and reactive oxygen species, would exhibit antidepressant activity.

There are evidences that cyclooxygenase (COX) and nitric oxide synthase (NOS) inhibitors have antidepressant-like activity. Drugs that reduce the neurotoxic challenge caused by proinflammatory cytokines, NO, prostaglandin E2 and other neurotoxins have potential antidepressant action. There is experimental evidence that the selective serotonin re-uptake inhibitor (SSRI) antidepressants, inhibit the release of TNF-α and NO from activated microglia. The activation of microglia by IFN-γ is associated with an influx of calcium ions that triggers the intracellular changes (phosphokinase C, p38, MAPK, ERK 1 and 2 and the JAK-STAT pathway) which result in the release of the proinflammatory cytokines. Thus by impeding the influx of calcium ions, the SSRI's reduce the activation of the JAK-STAT pathway and thereby reduce the inflammatory changes. These effects are unrelated to the action of the SSRIs on the serotonin transporter. [17]

This approach also helps to explain the chronic outcome of depression, particularly in elderly patients, where dementia frequently occurs as a consequence of the neurodegenerative cascade initiated by the proinflammatory cytokines, a reduction in neurotrophic factors (e.g. BDNF) due to hypercortisolaemia and an increase in reactive oxygen and nitrogen species. There is now evidence that the end products of the inflammation activated tryptophan–kynurenine pathway (such as 3-hydroxykynurenine and quinolinic acid) also play a substantial role in the neurodegenerative changes seen in chronic major depression. [13]

Limitations

The measurement of CRP was done on a single occasion, because it is a cross sectional study. So more research is needed to establish direct causal association with severity of depression.

Conclusion

It can be concluded that there is significant association between levels of CRP and severity of depression, not following normal distribution. Thus CRP levels can be helpful in diagnosis and furthur management of the disorder.

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