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Role of TNF and Hs CRP as novel biomarkers in etiopathogenesis of depression: A case-control study

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ABSTRACT

Introduction: Depression is a psychiatric disorder characterized by depressed mood, loss of interest in activities and loss of energy that lasts for two weeks or more. Depression affects individual emotional and psychological well-being with low self-esteem and ultimately resulted in social isolation. Nearly half of all cases of depression remain undetected for years or inadequately controlled. TNF-α has a vital role in inflammation, cell proliferation, differentiation, apoptosis, innate and adaptive immunity and have pathological role in several diseases. Early assessment of TNF-α and hs-CRP levels in depression patients could modify the disease progression and limit co-morbidities associated with it. Therefore, we assessed the level of TNF-α and hs-CRP in our study and correlated it with the disease severity.
Aim and Objectives: to study is to estimate TNF-α and hs-CRP levels in depressed patients and evaluate the relationship between the serum level of TNF- α and hs-CRP in the etiopathogenesis of depression.
Materials and Methods: This study was conducted at a tertiary level post graduate teaching institute of central India. 50 newly diagnosed drug naive cases of depression of age group 18-50 years, attending Psychiatry OPD. And 50 apparently healthy controls matched for same age and sex were taken. The subjects were enrolled for the study after taking ethics committee approval and obtaining written consent. The data collected was expressed as mean ± SD and analysed by using SPSS version 20. P-value of < 0.05 was accepted as statistically significant.
Result- The mean value of serum TNF-α among control group (11.209 ± 6.058 Pg/ml) which was lower as compared to case group (33.816 ± 21.581 Pg/ml). The difference among the two groups was found to be statistically significant as p value is less than 0.001. The mean Serum hs-CRP concentration was found to be higher in case group (7.524 ± 1.842 mg/l) as compare to control group (3.720 ± 1.238 mg/l). The difference among the two groups was found to be statistically significant as p value is <0.05. The difference among the three groups was found to be statistically significant as p value is less than 0.001. We observed a strong association between depression and increased serum TNF-α, with raised hs-CRP.
Conclusion: There are several researches potentiating the vital role of TNF- α and hs-CRPin depression. Large scale prospective studies are needed to establish the cause effect relationship and role of inflammatory cytokines in depression and to find newer treatment modalities like TNF-α blockers that might be helpful for consideration of new therapeutic approach Further studies are essential to detect the association. Nevertheless we found that depression might be responsible for elevated TNF-α and hs-CRP levels. We suggest screening of all the patients of depression for serum TNF-α estimation at initial OPD visit.

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1. Introduction

Depression is a psychiatric disorder characterized by depressed mood, loss of interest in activities and loss of energy that lasts for two weeks or more. Depression is one of the most common mood disorder which can manifest as a single episode or as recurrent episodes. Depression affects individual emotional and psychological well-being with low self-esteem and ultimately resulted in social isolation. Nearly half of all cases of depression remain undetected for years or inadequately controlled.[1]

When the depressive symptoms last for longer period with changes in appetite, sleep patterns and disturbances in daily activities then the diagnosis of depression must be considered. As the diagnosis of depression is done by ICD-10 depression diagnostic criteria, in all the cases of clinical depression, the criteria must be followed. In the ICD 10 criteria, list of ten depressive symptoms such as persistent low mood, loss of interest, low energy, disturbed sleep, poor concentration, low self confidence, poor or increased appetite, suicidal thoughts or acts, agitation and guilt. First three are key symptoms, others are associated symptoms a prognostic marker.

The word Depression originates from the Latin word deprimere. Deprimere means "press down."[2]

The Prevalence of depression worldwide, affecting up to 3.4% of the population. It is higher for women (4.1%) than for men (2.7%).[3] The lifetime prevalence of depression is 16.2%.[4] The prevalence of depression in India was 3.3% (3.1–3.6), in 2017 with the highest rate observed in Tamil Nadu, Kerala, Goa, and Telangana, Andhra Pradesh, and Odisha.[5]

More severe forms of depression can lead to suicide.[6] In chronic course of depression, impairment of an individual's occupational potential and quality of life occurs (QOL).[7]

Clinical depression is classified broadly into Mild (four symptoms), Moderate (five to six symptoms) and severe depression (seven or more symptoms).

Individuals with low quality of social relationships, have a high risk for future major depressive episodes.[7] Multiple studies across all over the world attempted to identify the exact etio-pathogenesis of depression, however exact pathogenesis of depression is unknown till date.[8] As several theories of etio-pathogenesis of depression have been proposed which include inflammatory hypothesis,[9] genetic factors,[10] monoamine hypothesis, endocrine hypothesis, probably contribute in variable proportions to the development & progression of depression.

TNF-α has a vital role in inflammation, cell proliferation, differentiation, apoptosis, innate and adaptive immunity and have pathological role in several diseases like cardiovascular diseases, diabetes, autoimmune diseases, osteoporosis and cognitive disorders Early assessment of TNF-α and hs-CRP levels in depression patients could modify the disease progression and limit co-morbidities associated with it. Therefore, we assessed the level of TNF-α and hs-CRP in our study and correlated it with the disease severity.

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2. Materials and Methods

The present study included 50 newly diagnosed drug naive cases of depression of age group 18-50 years, attending Psychiatry OPD in M.Y. Hospital and 50 apparently healthy controls matched for same age and sex were taken. The subjects were enrolled for the study after obtaining written consent.

2.1. Inclusion sriteria

1. Newly diagnosed and confirmed cases of depression.
2. Subjects in the age group of 18-50 yrs.
3. Patient ready to give written informed consent.

2.2. Exclusion criteria

1. Patients with atypical depression, recurrent depression, bipolar depression and any other psychiatric disorders.
2. Patients on antidepressant drugs.
3. Pregnant and lactating females.
4. Patients with any active infection, e g bacterial, viral, fungal.
5. Patients having dependence of alcohol or smoking.
6. Patients with any autoimmune inflammatory disease such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, diabetes etc.
7. Patients having mental retardation.
8. Patients having serious medical ailments (cancer, bed ridden patients.

2.3. Assessment of severity

Depression patients are assessed by Hamilton Rating Scale for Depression (HRSD) score. The serum levels of TNF-α and hs- CRP in patients of depression and apparently healthy control subjects and comparison between above two study groups were done using Thermofisher Scientific Multiscan FC ELISA Reader and BioSystem BA400 Biochemistry fully automated analyser, respectively.

2.4. Statistical analysis

Descriptive statistics was performed by using the proportional or frequency distribution of the parameters.

The frequency distribution was presented in form of tables along with graphical presentation of data. Frequency distribution was done for both qualitative data and categories of quantitative data.

2.5. Inferential statistical methods used

1. Student t test for two sample means was applied to calculate the significant difference the mean values of different numeric parameters of two groups.
2. One way ANOVA was applied to compare the mean difference between mean values of any parameters between three and more groups, followed by POST Hoc tukey test for individual group comparison.
3. Chi Square Test was applied to determine the association between two variables. The different parameter distribution was associated with different morbidities by using the Chi square test.

The P Value <0.05 will be considered as level of significance.

Microsoft Excel and R Studio (Open source analytical tool V 1.2.335) was used to perform the basic calculation, presentation and statistical analysis of data.

3. Results

The mean age of case group was 32.480 ± 10.176 years while that of control group was 35.100 ± 8.922 years.

Among the cases maximum 38% belonged to 21-30 year age group and 28% belonged to 31-40 year age group. Among all 100 participants, female participants were 55 (55%) and male participants were 45(45%). Among all subjects, maximum 67% were married. Marital status wise distribution among cases and control group was nearly equal. In control group maximums (76%) were educated higher secondary and above in contrast to case group which were 36%.

In occupation, among cases maximum 58% were unemployed as compared to control group which were 20%, among control maximum 40% were professional while in case group only 4% were professional.

Maximum no. of case group (60%) were belongs to low socioeconomic group while in control group maximum (58%) belongs to upper socioeconomic group. who also found that lower than expected educational attainment are significantly associated with depression and more common in low social class, unemployed condition, low educational level. mong cases (38%) and control (41%) groups maximum belonged to nuclear type families.

3.1. BMI and depression

The mean BMI of depressive group was 21.94 ±1.168 kg/m^2 while that of control group was 20.420 ± 0.575 kg/m^2.

3.2. hs-CRP and depression

In our study serum hs-CRP levels were found significantly increased (p value 0.001) in all the depression patients as compared to controls. The mean serum hs-CRP levels in case group (group 7.524 ± 1.842mg/l) was higher than in control group (3.720 ± 1.238mg/l).

3.3. Correlation of hs-CRP and depression

The serum hs-CRP levels has shown positive and statistically significant correlation with severity of disease. Out of the 50 patients, 25 (50%) patients have mild degree of depression with mean hs-CRP levels 6.084 ± 0.759 mg/l and 21 patients (42%) had moderate degree of depression with mean hs-CRP levels 8.709 ± 1.112 mg/l and 4 patients (8%) had severe degree of depression with mean hs-CRP levels 10.300 ± 2.227 mg/l signifying that as severity of depression increases hs-CRP level increases. The highest mean hs-CRP levels were seen in severe depression while levels were lowest in mild depression.

3.4. TNF-α and depression

In our study serum TNF-α levels were found significantly increased (p value 0.000) in all the depression patients as compared to controls. The mean serum TNF-α levels in case group (33.816 ± 21.581pg/ml) was higher than in control group (11.209 ± 6.058 pg/ml).

3.5. Correlation of TNF-α and depression

In our study as severity of depression increased as the HAMD score increased and consequently TNF-α levels were also raised. Out of the 50 patients, 25 (50%) patients have mild degree of depression with mean TNF-α levels 15.228 ± 3.186 pg/ml and 21 patients (42%) had moderate degree of depression with mean TNF-α levels 46.714 ± 7.061pg/ml and 4 patients (8%) had severe degree of depression with mean TNF-α levels 82.275 ± 4.345 pg/ml signifying that as severity of depression increases TNF-α level increases.

4. Discussion

Among the cases maximum 38% belonged to 21-30 year age group and 28% belonged to 31-40 year age group. These results are consistent with previous finding by R. Ponnudurai et al., who found that peak incidence of depression was observed in the age group of 26-45 years. The female participants were outnumbered as compared to male participants. Among all 100 participants, female participants were 55 (55%) and male participants were 45(45%). Patten SB, Wang JL, Williams JV, et al. 2006also reported similar results that major depression was more common in women than in men.[7] Among all subjects, maximum 67% were married. Marital status wise distribution among cases and control group was nearly equal. This result is consistent with Sharma et al. 1985, who also found depression more common in married subjects. In cases on religion wise distribution 84% were Hindus and in

Table 1: Comparison of mean serumTNF-α

Variable	HAM-D Grade	N	Mean	Std. Deviation	F Test	P Value	Result
Serum TNF-α (pg/ml)	Mild	25	15.228	3.186	389.794	0.001	Significant
	Moderate	21	46.714	7.061			
	Severe	4	82.275	4.345			
	Total	50	33.816	21.581			

Table 2: Hs CRP in patients based on HAM-D grade

Variable	HAM-D Grade	N	Mean	Std. Deviation	F Test	P Value	Result
Serum hs-CRP (mg/l)	Mild	25	6.084	0.759	48.68	0.001	Significant
	Moderate	21	8.709	1.112			
	Severe	4	10.300	2.227			
	Total	50	7.524	1.842			

control 92% were Hindu.[2,8] Among subjects more Hindus were diagnosed with depression while less Muslim subjects (16%) were suffering from depression. Study done by Nandi DN et al. 1979,[5] states that depressive disorder is common among Muslim region. However we could not infer from this result finding as Hindu subjects outnumbered to Muslim subjects. This can also be attributed to demographic bias. In control group (76%) were educated higher secondary and above in contrast to case group which were 36%. In occupation, among cases maximum 58% were unemployed as compared to control group which were 20%, among control maximum 40% were professional while in case group only 4% were professional. Maximum no. of case group (60%) were belongs to low socioeconomic group while in control group maximum (58%) belongs to upper socioeconomic group. These results is also supported by study of Ramachandran V. et al. 1982. D.K. Sharma et al. 1985, Tiwari SC 2000and Jain RK et al. in 2007, who also found that lower than expected educational attainment are significantly associated with depression and more common in low social class, unemployed condition, low educational level.[1,3] Among cases (38%)and control (41%) groups maximum belonged to nuclear type families. Many studies Lai, 1971, Bagadia, 1973 and Sethian d Sinha, 1977 and Sethi BB 1980, have demonstrated association between depression and family constellation. Maximum subjects in cases (74%) and control group (64%) belonged to urban locality. Similar result by Nandi PS 1997and Reddy VM et al 1998, confirmed higher prevalence of depression for urban sector.[5]

hs-CRP and Depression: In our study serum hs-CRP levels were found significantly increased (p value 0.001) in all the depression patients as compared to controls. The mean serum hs-CRP levels in case group (group7.524 ± 1.842mg/l) was higher than in control group (3.720 ± 1.238mg/l).M. Bryant Howren et al., who also found that serum hs-CRP level was positively and statistical significantly associated with depression.[9]

4.1. Correlation of hs-CRP and Depression

The serum hs-CRP levels has shown positive and statistically significant correlation with severity of disease. Out of the 50 patients, 25 (50%) patients have mild degree of depression with mean hs-CRP levels 6.084 ± 0.759 mg/l and 21 patients (42%) had moderate degree of depression with mean hs-CRP levels 8.709 ± 1.112 mg/l and 4 patients (8%) had severe degree of depression with mean hs-CRP levels 10.300 ± 2.227 mg/l signifying that as severity of depression increases hs-CRP level increases. The highest mean hs-CRP levels were seen in severe depression while levels were lowest in mild depression. This result is also supported by study of Yung et al.,[10] who found that serum level of hs-CRP was higher in patients with more Beck Depression Inventory score.

4.2. TNF-α and depression

In our study serum TNF-α levels were found significantly increased (p value 0.000) in all the depression patients as compared to controls. The mean serum TNF-α levels in case group (33.816 ± 21.581pg/ml) was higher than in control group (11.209 ± 6.058 pg/ml).

4.3. Correlation of TNF-α and depression

In our study as severity of depression increases as HAMD score increase consequently TNF-α levels increases. Out of the 50 patients, 25 (50%) patients have mild degree of depression with mean TNF-α levels 15.228 ± 3.186 pg/ml and 21 patients (42%) had moderate degree of depression with mean TNF-α levels 46.714 ± 7.061pg/ml and 4 patients (8%) had severe degree of depression with mean TNF-α levels 82.275 ± 4.345 pg/ml signifying that as severity of depression increases TNF-α level increases. This result was consistent with previous study by Wei Zou et al. who found that serum levels of TNF-α significantly correlated with severity of depression ($p < 0.05$) on HAMD rating scale of depression and higher TNF-α levels were associated with higher HAMD scores.[10]

There are several researches potentiating the vital role of TNF- α and hs-CRP in depression. In cases of moderate to severe depression the TNF-α levels are found significantly increased as compared to cases of mild depression. So TNF-α levels have positive correlation with the disease severity. This increased TNF-α levels can be a cause for occurrence or progression of depression because of its direct effect on TNF-α Receptors on cells of immune system or it could be an effect of disease which because of autoimmune and inflammatory destruction of brain cells ultimately results in increased synthesis of TNF-α.Patients of depression also have markedly raised serum levels of hs-CRP as compared to controls and also has a positive correlation with the disease severity.

Our study has also explored the possible association between these biochemical parameters in patients with disease activity. Till date anti TNF-α analogues are not routinely used along with antidepressant drugs as a major treatment modality in depression because its potential role in systemic therapy for depression is still not very much evident. Thus we suggest that TNF-α evaluation at the time of diagnosis in patients of depression and use of TNF-α antagonists that might improve the outcome of this psychologically devastating disease and reduce the severity and progression

5. Conclusion

On the basis of results of the our study, we can conclude that the patients of depression have raised TNF-α and hs-CRP levels as compared to normal healthy control group. Large scale prospective studies are needed to establish the cause effect relationship and role of inflammatory cytokines in depression and to find newer treatment modalities like TNF-α blockers that might be helpful for consideration of new therapeutic approach Further studies are essential to detect the association. Nevertheless, we found that depression might be responsible for elevated TNF-α and hs-CRP levels. We suggest screening of all the patients of depression for serum TNF-α estimation at initial OPD visit.

6. Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

7. Source of Funding

None.

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