ORIGINAL ARTICLE

The Association of Pro-inflammatory Markers with Suicidality in Patients Suffering from Major Depressive Episode

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ABSTRACT

Objective: To determine the association of pro-inflammatory markers with suicidality in patients suffering from major depressive episode.

Study Design: Descriptive cross sectional study.

Place and Duration of Study: The study was conducted at department of pathology in collaboration with the department of psychiatry, Pakistan Railway Hospital, Islamic International Medical College, Rawalpindi from 18th April, 2017 to 17th March, 2018.

Materials and Methods: Seventy five subjects recruited through convenient non-probability sampling technique were divided into three groups i.e. Group 1 (patients of major depressive episode with suicidality), Group 2 (patients of major depressive episode without suicidality) and Group 3 included healthy controls. Patients of major depressive episode and suicidality were diagnosed through Hamilton rating scale for depression and beck scale for suicidal intention successively. Pro-inflammatory markers i.e. Interleukin-1ß, Interleukin-6 and C-reactive protein were measured in the serum of all participants. Data was analyzed through statistical package for social sciences version 21. Simple descriptive statistics (frequencies, percentages) were computed for each categorical variable. Mean and standard deviation were calculated for the numerical data. Independent t test and one way ANOVA was applied to determine the statistical significance. *P* value of < 0.05 was considered significant.

Results: Out of 75 enrolled patients, Pro-inflammatory markers i.e. Interleukin-1ß, Interleukin-6 and C-reactive protein were raised in patients of major depressive episode with suicidality.

Conclusion: Pro-inflammatory markers i.e. CRP, IL-1ß and IL-6 are markedly raised in patients of major depressive episode with suicidality. So, from the results it is concluded that pro-inflammatory markers have an association with suicidality in patients of major depressive episode and treating inflammation in them can improve their symptoms and reduce suicidal rate.

Key Words: *CRP, IL-1ß, IL-6, Inflammation, Major Depressive Episode, Pro-inflammatory Markers and Suicidality*

Introduction

Suicide is the second major cause behind the death of youngsters among the 15–29 age group in the world.[1] According to one estimation, 40,000 people die of suicide per year in the United States and the global death rate was nearly 800000 in the year 2014 calculated by World Health Organization (WHO).[1] It was predicted by WHO in 2011 that one million people would die by the year 2030 due to suicide, that will contribute to 1.4% of all the deaths globally.[1] The real number of deaths may be higher because suicidal deaths are normally not reported due to societal issues and criminalization of suicide in many societies.[1] Suicidal attempts are also insufficiently reported. Almost twenty or more than that suicide attempts occur for every completed suicide, so suicide attempts are more frequent than completed suicide.[1] There is emerging evidence that this behavioral phenotype is independently associated with a pro-inflammatory state in the body, and that it is not linked to the severity of depression per se.[2]

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Many studies have shown that suicide is associated with an increase in inflammatory markers in the body.[2] **"Cytokine-induced sickness behavior"** (i.e., lethargy, fatigue, depression, failure to concentrate, anorexia, sleep problems, reduced sense of personal hygiene and social withdrawal) has been shown to be linked and mediated by pro-inflammatory cytokines i.e. IL-1 and IL-6.[3] Another important mechanism underlying suicidality is the activation of kynurenine pathway for the catabolism of tryptophan. Abnormalities in this pathway lead to certain biological mechanism which associates inflammation with suicidality and depression.[4] Tryptophan catabolism through kynurenine pathway produces certain neuroactive substances especially quinolinic acid (QUIN) and kynurenic acid (KYNA).[5] The inflammatory cytokines especially IL-1ß, IL-6 and IFN-**γ** are potent activators of indole amine 2, 3 dioxygenase (IDO-1) and tryptophan 2.3 dioxygenase (TDO2). These two enzymes regulate the initial steps in kynurenine pathway.[6,7] Tryptophan is the precursor of serotonin neurotransmitter, so catabolism of tryptophan through this pathway down regulates the amount of serotonin in the body.[8] This mechanism can directly lead to lower levels of monoamines in the CSF and serum of suicidal victims.[1] A meta-analysis by Black & Miller published in 2015 has shown that levels of IL-1 β, IL-6 & TNF-α are elevated in the body fluids of those psychiatric patients who attempted suicide or have strong suicidal ideation.[2] Identification of specific inflammatory markers and important co-existing biological factors can inform us regarding the risk of suicidal behavior. Further, treatments targeting the constituents of the inflammatory pathway are nowadays undergoing trials for a variety of psychiatric conditions, and this approach can lead to the development of novel therapeutic tools for the prevention of suicide.[9] Our proposition is that patients who contemplate or attempt suicide have an inflammatory state in their bodies which can be detected by measuring pro-inflammatory markers like interleukin-1 β, interleukin 6 and C-reactive protein (CRP) in the serum.[10,2] In the extant literature review, no single study has documented the association of IL-1 β, IL-6 & C-reactive protein together with the existence of suicidality.[2] Further, no local studies are available to relate the association of pro-inflammatory markers with suicidality in patients of major depressive episode (MDE) patients. The objective of our study is to find the association of pro-inflammatory markers (IL-1β, IL-6 & CRP) with suicidality in patients suffering from major depressive episode (MDE).

Materials and Methods

This observational cross sectional study was conducted at Chemical Pathology department in collaboration with psychiatry department of Pakistan Railway Hospital, Islamic International Medical College, Rawalpindi from 18th April, 2017 to 17th April, 2018 after getting permission from ethical review committee of Riphah International University. Sample size was decided based on the data from similar previous studies. Participants from both genders were enrolled through non-probability convenient sampling after taking informed consent. Seventy-five participants were inducted in the study between the ages of 18 to 65 years and divided into three groups each having twenty-five participants. Group 1 had twenty-five patients of major depressive episode (MDE) with suicidality, Group 2 had twenty-five patients of MDE without suicidality and Group 3 had twenty-five healthy adults. Participants having any acute or chronic infection or inflammation, obesity, allergies, pregnancy and lactating mothers were excluded. Participants of MDE and suicidality were diagnosed based on Hamilton rating scale for depression (HRSD) and Beck Scale for suicidal intent respectively by a qualified Psychiatrist in OPD of psychiatry department. After filling demographic data, patients were directed towards Pathology lab and 5 ml of venous blood was withdrawn in plain vacutainers considering all necessary measures to avoid pre-analytical errors. Samples were transported in crushed ice to CREAM lab of Army Medical College, Rawalpindi for refrigerated centrifuge at 4° C. Serum was extracted and stored at -80° C. CRP levels of all samples were analyzed through visual agglutination semi quantitative method. IL-1ß and IL-6 were analyzed by ELISA method. Data was analyzed through statistical package for social sciences (SPSS) version 21. Simple descriptive statistics (frequencies, percentages) were computed for each categorical variable. Mean and standard deviation were calculated for numerical data. Independent *t* test and one way

ANOVA were applied to determine the statistical significance. *P* value of < 0.05 was considered significant.

Results

Total 75 patients were divided into three equal group i.e. group 1 consisted of patients of MDE with suicidality, group 2 consisted of MDE patients without suicidality and group 3 consisted of healthy adults with no history of somatic or psychiatric illness.

Descriptive statistics of age (years) was calculated in terms of mean and standard deviation. Mean age (years) of participants was overall 33.32±8.93 whereas mean age (years) of MDE patients with suicidality was 28.44±6.70 and of MDE patients without suicidality was 37.8±8.10. The mean age (years) of healthy adults was 33.72±8.93. Distribution of gender was calculated in terms of frequency and percentage of male and female patients. There were 39 (52.0%) male participants, of these 11 (44.0%) were present in group 1 (MDE with suicidality), 13 (52.0%) male patients were included in group 2 (MDE without suicidality) and 15 (60.0%) male participants were present in group 3 (Healthy adults). There were 36 (48.0%) female participants included in the study, of these 14 (56.0%) were present in group 1 (MDE with suicidality), 12 (48.0%) female patients were included in group 2 (MDE without suicidality) and 10 (40.0%) were present in group 3 (Healthy adults). The association of pro-inflammatory markers (IL-1 β, IL-6 and CRP) with suicidality in patients suffering from major depressive episode (MDE) was assessed using independent *t* test. The results came out to be statistically significant for all the three markers i.e. P-value < 0.05 as shown in Table I and Table II.

Pro-inflammatory markers (CRP, IL-1ß and IL-6) were compared among three groups using one way ANOVA. The results showed statistically significant difference for all pro-inflammatory markers (p value<0.001) as shown in Table III.

Table I: Comparison of Pro-inflammatory Markers between Groups 1 and Group 2

Pro-inflammatory Markers	GROUPS		P-value*
	Group 1* n=25	Group 2** n=25	
CRP level (mg/L)	6.48±5.36	3.04±2.38	0.005
IL-1β (pg/ml)	30.71±40.16	0.73±1.29	0.001
IL-6 (pg/ml)	134.76±157.08	9.95±5.75	<0.001

P≤0.05 was taken as level of significant
Group 1: MDE with suicidality
Group 2: MDE without suicidality

Table II: Comparison of Pro-inflammatory Markers between Groups 1 and Group 3

Pro-inflammatory Markers	GROUPS		P-value*
	Group 1* n=25	Group 3** n=25	
CRP level (mg/L)	6.48±5.36	2.0±0.0	<0.001
IL-1β (pg/ml)	30.71±40.16	0.42±0.88	<0.001
IL-6 (pg/ml)	134.76±157.08	0.31±1.02	<0.001

P≤0.05 was taken as level of significance
Group 1: MDE with suicidality
Group 3: Healthy Adults

Table III: Comparison of Pro-inflammatory Markers among Three Groups (n=75)

Pro-inflammatory Markers	GROUPS			P-value *
	Group 1 n=25	Group 2 n=25	Group 3 n=25	
CRP level (mg/L)	6.48±5.36	3.04±2.38	2.0±0.0	<0.001
IL-1β (pg/ml)	30.71±40.16	0.73±1.29	0.42±0.88	<0.001
IL-6 (pg/ml)	134.76±157.08	9.95±5.75	0.31±1.02	<0.001

P≤0.05 was taken as level of significant

Discussion

The results of present study show that in healthy adults, levels of cytokines are undetectable. In 2013, Kleiner et al. also published a study in which it was concluded that in normal healthy people levels of cytokines were undetectable due to the absence of any inflammatory stimulus.[9] Due to the absence of inflammation in healthy adults, CRP levels are also undetectable or within normal range in them.

In patients of major depressive episode without suicidality, the levels of pro-inflammatory markers like interleukin-1ß, interleukin-6 were high as compared to healthy adults. This shows that some degree of inflammation is also present in patients of major depressive episode irrespective of absence of

suicidality in them. However, the levels are not as much elevated as in patients of major depressive episode with suicidality. In 2013, a study conducted by Valkanova V et al. also concluded that levels of CRP and IL-6 were high in depressed patients.[10] In 2007, a study conducted by Kim YK et al. also showed that levels of cytokines were high in depressed patients.[14] Hughes MM et al. also found out during their study that inflammation and inflammatory markers play a vital role in the pathogenesis of depression and therapies targeting this inflammation might prove beneficial.[11] In 2005, Schiepers OJ et al. published their review article regarding cytokines and depression. They concluded after reviewing many studies related to the subject that cytokines play a pivotal role in the central regulation of certain behavioral changes linked to depression.[12]

In this study it is observed that suicidality in MDE patients is not directly linked to the severity of depression. Another important finding is that certain behavioral traits like aggression, loss of hope and hostile behavior are specially highlighted in patients of MDE with suicidality as compared to MDE patients without suicidality. In 2006, Brezo J et al. reviewed some studies and concluded similar finding that certain behavioral traits were linked to suicidality directly.[13] In 2015, DeShong HL et al. presented a "five factors model" which was based on similar personality traits. They concluded that these behavioral traits could predict future risk of suicidality in MDE patients.[14] So, these findings during this study are in accordance to the previous studies.[13, 14] Importantly among these behavioral aspects "**Hopelessness"** which is a very important factor in diagnosing psychiatric patients especially with suicidality was previously identified to be associated with raised interleukin-6 levels and this finding is also observed and concluded in this study.[15]

CRP was markedly raised in patients of suicidality when compared to non-suicidal depressed patients and healthy individuals. This shows that level of inflammation is higher in patients of suicidality as compared to the non-suicidal depressed patients. Courtet at al. also worked on CRP in both patients with suicidality and non-suicidality and found that high CRP levels were associated with suicidality in MDE patients. They also found that irrespective of low or high risk for suicidality, CRP levels were raised in acute cases. [16] In another recent study, Gibbs et al. did research work on indoor psychiatric patients with and without suicidal behavior. They found out that MDE patients with high degree of suicidality had greater inflammation and increased levels of CRP when compared to MDE patients without suicidality and healthy adults.[17] In 2015, Black and Miller in their meta-analysis of many studies based on inflammation and suicidality also concluded that inflammation was strongly associated with suicidality in MDE patients.[2]

Conclusion

It is concluded that pro-inflammatory markers are significantly high in MDE patients with suicidality. This also throws light on the association of pro-inflammatory markers with suicidality and importance of treating patients with anti-inflammatory drugs in medicine resistant depression with suicidality.

Limitations

This study was conducted in a single outdoor patient department. Due to financial constraints and limited time duration availability, a small group of patients was included. There are some other pro-inflammatory markers and anti-inflammatory markers mentioned in literature like TNF-α, IL-2 etc. They can be considered for further studies. A longitudinal study can be conducted in future to observe the effect of anti-inflammatory drugs in these patients.

REFERENCES

1. Brundin L, Bryleva EY, Thirtamara Rajamani K. Role of Inflammation in Suicide: From Mechanisms to Treatment. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2017;42(1):271-83.
2. Black C, Miller BJ. Meta-Analysis of Cytokines and Chemokines in Suicidality: Distinguishing Suicidal Versus Nonsuicidal Patients. Biological psychiatry. 2015;78(1):28-37.
3. Courtet P, Giner L, Seneque M, Guillaume S, Olie E, Ducasse D. Neuroinflammation in suicide: Toward a comprehensive model. The World Journal of Biological Psychiatry. 2016;17(8):564-86.
4. Lotrich FE, Ferrell RE, Rabinovitz M, Pollock BG. Labile anger during interferon-alpha treatment is associated with a polymorphism in tumor necrosis factor-alpha. Clinical neuropharmacology. 2010;33(4):191-7.
5. Schwarcz R, Bruno JP, Muchowski PJ, Wu HQ. Kynurenines in

the mammalian brain: when physiology meets pathology. Nature reviews Neuroscience. 2012;13(7):465-77.

6. Schwieler L, Larsson MK, Skogh E, Kegel ME, Orhan F, Abdelmoaty S, et al. Increased levels of IL-6 in the cerebrospinal fluid of patients with chronic schizophrenia--significance for activation of the kynurenine pathway. Journal of psychiatry & neuroscience : JPN. 2015;40(2):126-33.
7. Urata Y, Koga K, Hirota Y, Akiyama I, Izumi G, Takamura M, et al. IL-1beta increases expression of tryptophan 2,3-dioxygenase and stimulates tryptophan catabolism in endometrioma stromal cells. American journal of reproductive immunology (New York, NY : 1989). 2014;72(5):496-503.
8. Maes M, Leonard BE, Myint AM, Kubera M, Verkerk R. The new '5-HT' hypothesis of depression: cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. Progress in neuro-psychopharmacology & biological psychiatry. 2011;35(3):702-21.
9. Kleiner G, Marcuzzi A, Zanin V, Monasta L, Zauli G. Cytokine levels in the serum of healthy subjects. Mediators of inflammation. 2013;2013:434010.
10. Valkanova V, Ebmeier KP, Allan CL. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. Journal of affective disorders. 2013;150(3):736-44.
11. Hughes MM, Connor TJ, Harkin A. Stress-Related Immune Markers in Depression: Implications for Treatment. The international journal of neuropsychopharmacology. 2016.
12. Schiepers OJ, Wichers MC, Maes M. Cytokines and major depression. Progress in neuro-psychopharmacology & biological psychiatry. 2005;29(2):201-17.
13. Brezo J, Paris J, Turecki G. Personality traits as correlates of suicidal ideation, suicide attempts, and suicide completions: a systematic review. Acta psychiatrica Scandinavica. 2006; 113(3):180-206.
14. DeShong HL, Tucker RP, O'Keefe VM, Mullins-Sweatt SN, Wingate LR. Five factor model traits as a predictor of suicide ideation and interpersonal suicide risk in a college sample. Psychiatry research. 2015;226(1):217-23.
15. Mitchell AM, Possel P, Sjogren E, Kristenson M. Hopelessness the "active ingredient"? Associations of hopelessness and depressive symptoms with interleukin-6. International journal of psychiatry in medicine. 2013;46(1):109-17.
16. Courtet P, Jaussent I, Genty C, Dupuy AM, Guillaume S, Ducasse D, et al. Increased CRP levels may be a trait marker of suicidal attempt. European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology. 2015; 25(10):1824-31.
17. Gibbs HM, Davis L, Han X, Clothier J, Eads LA, Caceda R. Association between C-reactive protein and suicidal behavior in an adult inpatient population. Journal of psychiatric research. 2016; 79:28-33.