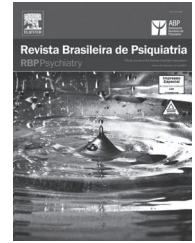




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BRIEF COMMUNICATION

Peripheral chemokine levels in women with recurrent major depression with suicidal ideation

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DESCRIPTORS

Suicide;
Suicidal Ideation;
Chemokines;
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Major Depressive Disorder;
Mood Disorders;
Inflammation;
Immunity.

Abstract

Objective: To compare serum levels of MCP-1/CCL2, RANTES/CCL5, and Eotaxin/CCL11 between female patients with recurrent major depressive disorder (MDD) and healthy controls, verifying if there is a difference in the levels of these mediators between those with or without current suicidal ideation. **Methods:** Thirty female outpatients with recurrent MDD were divided in two groups accordingly the presence or absence of suicidal ideation. These groups were compared with 16 healthy controls. Serum levels of MCP-1/CCL2, RANTES/CCL5, and Eotaxin/CCL11 were determined. Depression severity was evaluated by Beck Depression Inventory (BDI). Suicidal ideation was assessed by SCID-I and BDI. **Results:** Patients with recurrent MDD and healthy controls did not differ in age, socioeconomic status, and education. All patients reported high scores of BDI (mean, SD, n; 29.75, 10.55, 28). Multivariable analysis of covariance adjusted for age and BMI showed that MDD patients with suicidal ideation presented lower levels of MCP-1/CCL2 and RANTES/CCL5 ($p < 0.001$) and higher levels of Eotaxin/CCL11 ($p = 0.04$) compared to healthy controls. These differences remained significant after adjusting for depression severity. **Conclusion:** The findings of this study indicated that the presence of recurrent MDD with suicidal ideation is associated with differences in inflammatory chemokines when compared to those without suicidal ideation.

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DESCRITORES:

Suicídio;
 Ideação suicida;
 Quimiocinas;
 Citocinas;
 Transtorno Depressivo
 Maior;
 Transtornos do Humor;
 Inflamação;
 Imunidade.

Níveis periféricos de quimiocina em mulheres com depressão maior com ideação suicida

RESUMO

Objetivo: Comparar os níveis séricos de MCP-1/CCL2, RANTES/CCL5 e Eotaxin/CCL11 entre pacientes do sexo feminino com transtorno depressivo maior (TDM) recorrente e controles saudáveis, verificando se há diferença nos níveis desses mediadores entre os indivíduos com ou sem ideação suicida. **Métodos:** Trinta pacientes do sexo feminino com TDM recorrente foram divididas em dois grupos de acordo com a presença ou ausência de ideação suicida. Esses grupos foram comparados com 16 controles saudáveis. Os níveis séricos de MCP-1/CCL2, RANTES/CCL5 e Eotaxin/CCL11 foram determinados. A gravidade da depressão foi avaliada usando o *Beck Depression Inventory* (BDI) e a ideação suicida foi avaliada usando o SCID-I e o BDI. **Resultados:** As pacientes com TDM recorrente e os controles saudáveis não diferiram em idade, *status* socioeconômico e educação. Todas as pacientes relataram altas pontuações no BDI (média, SD, n; 29,75, 10,55, 28). A análise de covariância multivariada ajustada para idade e de IMC mostrou que as pacientes com TDM e ideação suicida apresentaram níveis mais baixos de MCP-1/CCL2 e RANTES/CCL5 ($p < 0,001$) e níveis mais elevados de Eotaxin/CCL11 ($p = 0,04$) em comparação com os controles saudáveis. Essas diferenças permaneceram significantes após o ajuste para gravidade da depressão. **Conclusão:** Os resultados deste estudo indicaram que a presença de TDM recorrente com ideação suicida está associada a diferenças nas quimiocinas inflamatórias na comparação com os indivíduos sem ideação suicida.

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Introduction

Suicide is a major problem in public health, with approximately 1 million people dying from suicide per year.¹ Mental illnesses, particularly major depressive disorder, (MDD) are the main risk factor for suicide. Although several factors including personality and cultural and ethnic background may exert influence on suicidality of depressed patients, neurobiological factors involved in suicidal ideation and behavior has received considerable attention. Several studies have documented different biological changes in subgroups of individuals with MDD and suicidal behavior,² including serotonergic and noradrenergic system abnormalities. Hypothalamus-pituitary-adrenal (HPA) axis dysfunction has also been reported.

A growing body of evidence has indicated the presence of a longstanding pro-inflammatory state in MDD. Increases in inflammatory mediators such as cytokines were extensively shown in MDD, with interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α) and interleukin-1 (IL-1) being the most commonly associated with MDD.³⁻⁵ The causes for this pro-inflammatory state are largely unknown, although both genetic and environmental factors have been proposed as relevant.⁶ Chemokines, cytokines with chemoattractive properties, have received less attention regarding their role in MDD. Nevertheless, these inflammatory mediators may be of particular interest in these patients, given their effect on the amplification of inflammatory response, possibly resulting in increased neuronal and glial death.^{3,7-9} For instance, peripheral chemokine levels seem to be altered in neurodegenerative disorders, such as multiple sclerosis¹⁰ and Alzheimer's disease^{11,12} and in neuropsychiatric disorders such as schizophrenia^{13,14}

and bipolar disorder.¹⁵ To date, more than 50 chemokines and approximately 20 chemokine receptors, particularly G-protein-coupled receptors,¹⁶ have been identified. The two largest families of chemokines, CCL and CXCL, attract mononuclear cells to sites of chronic inflammation. The binding of a chemokine to its receptor activates signaling cascades that lead to cell shape rearrangement and movement,¹⁷ namely chemokine (C-C motif) ligand 11 (Eotaxin/CCL11).¹⁸ Activation of these signaling pathways results in increased calcium concentrations and activation of mitogen-activated protein kinases, and also has a role in synaptic plasticity.¹⁶ For instance, CCL and CXCL chemokines have been shown to help in the prevention of neuronal apoptosis.^{19,20} Monocyte chemoattractant protein-1 (MCP-1/CCL2) and regulated-on-activation normal T cell expressed and secreted (RANTES/CCL5) protein are important mediators of the immune and inflammatory responses.²¹

Studies exploring differences in inflammatory mediators across subgroups of depressive patients are scarce. A recent report indicated differences in cytokine concentrations among suicide attempters compared to non-suicidal depressed patients and healthy controls.²² Suicide attempters have increased levels of IL-6 and TNF- α as well as decreased levels of IL-2 concentrations. Unfortunately there are very few studies investigating the role of chemokines in major depression and suicide.²³

Because understanding the inflammatory mechanisms involved in MDD and suicide may potentially open new treatment possibilities, the aim of this study was to investigate chemokine differences between MDD individuals with and without suicidal ideation, in order to propose novel markers of suicidal ideation in MDD.

Methods

Thirty patients with recurrent MDD were recruited from a specialized outpatient clinic (Mood Disorders Program) at Hospital Presidente Vargas, Porto Alegre, Brazil. Psychiatric diagnosis was based on application of the Structured Clinical Interview for DSM-IV-Axis I Disorders (SCID-I). Depression severity was evaluated by Beck Depression Inventory (BDI). Suicidal ideation (SI) was assessed by SCID-I (“Over the last month: Have you wished you were dead?”; “Have you wanted to harm yourself?”; “Have you thought of committing suicide?”; and “Have you planned how to commit suicide?”) and BDI (“I have thoughts about committing suicide but I would not carry them out”; “I have definite plans about committing suicide”; “I would kill myself if I could”). Outpatients were classified according to whether they reported in both instruments to have (n = 18) or have not (n = 12) suicidal ideation. All patients had been using a stable dosage of antidepressant monotherapy at least for 3 months and were free of other medications for 4 weeks before blood collection. Exclusion criteria were: axis I comorbidities; severe or unstable clinical illness or illness associated with reports on abnormal immunological parameters; body mass index (BMI) above 30 kg/m²; neurological disorder; psychotic symptoms or any psychoactive substance used in past 30 days (except nicotine, caffeine, and antidepressants); current use of corticosteroids or nonsteroidal anti-inflammatory drugs; and acetylsalicylic acid or immunosuppressives.

Sixteen healthy volunteers were matched by age, social status, and BMI in MDD patients. Healthy control group was screened for psychiatric disorders using the non-patient version of SCID-I. Subjects included in the study were not using any medication, and their first-degree relatives had no history of major psychiatric disorders, dementia, mental retardation, cancer, or tumor. Exclusion criteria for healthy subjects were the same as those used in the selection of MDD patients. All participants had their socioeconomic status (SES) rated by the Hollingshead Index based on marital status, gender, occupation, and education.²⁴

Five milliliters of blood were collected from each subject by venipuncture in EDTA tubes. Samples were immediately centrifuged at 3000g for 5 min, and plasma was kept frozen at -80 °C until assayed. Plasma concentration of chemokines was determined using sandwich ELISA kits, following the

manufacturer’s protocol (R&D Systems, Minneapolis, MN, USA). All samples were assayed in duplicate. Assay detection limit was 5 pg/mL.

Statistics

Descriptive analyses included assessment of the distribution of all variables; data are presented as means and percentages. Demographic and clinical characteristics were analyzed using the χ^2 -test and analysis of variance (ANOVA), as indicated. Chemokine levels showed a non-parametric distribution and were analyzed after log transformation. Multivariate analysis of covariance (MANCOVA) was employed to compare mean differences between groups adjusting for those variables with significant differences in univariate ANOVAs. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Demographic and clinical characteristics of the sample (n = 49) are presented in Table 1. Both groups were homogeneous in terms of age, socioeconomic status, and education. All patients reported high scores of BDI (mean, SD, n; 29.75, 10.55, 28) presenting 11.5 years of illness duration (SD 5.58) and no medical comorbidities. As expected, outpatients with MDD and SI presented higher scores of depression severity. There were no differences between MDD with SI versus MDD without SI groups regarding the use of tricyclics (50% vs. 41.7%, $p = 0.71$), selective serotonin reuptake inhibitors (39% vs. 50%, $p = 0.72$), or other antidepressants use (11.1% vs. 8.3%, $p = 0.99$). The type of antidepressant had no influence on CCL2, CCL5, and CCL11 plasma levels ($F = 2.52$, $p = 0.743$) among MDD patients.

Multivariable analysis of covariance adjusted for age and BMI showed that MDD with SI presented lower levels of MCP-1/CCL2 and RANTES/CCL5 compared with MDD without SI and controls. Higher levels of Eotaxin/CCL11 in MDD with SI and MDD without SI were identified when compared to healthy controls. All differences remained significant after adjusting for depression severity (Figure 1). Assumptions for MANCOVA were tested and met. Independence was met through the study design; multivariate normality and linearity were assessed

Table 1 Clinical and demographic characteristics of the sample and results of chemokine measurements

	Healthy Control (n = 16)	Non-suicidal Ideation (n = 12)	Suicidal Ideation (n = 18)	p	Post hoc test ^c
Age (years)	38.12 (3.87)	37.75 (9.45)	40.17 (8.25)	0.643	HC = NSI = SI
Education (years)	8.56 (2.55)	8.58 (4.4)	7.83 (3.51)	0.783	HC = NSI = SI
BMI ^a	25.80 (1.73)	24.97 (2.42)	26.28 (2.10)	0.27	HC = NSI = SI
BDI ^b	5.12 (3.87)	20.83 (9.36)	33.61 (9.51)	< 0.0001	HC < NSI < SI
CCL2 (pg/mL)	536.74 (184.12)	523.94 (212.88)	353.97 (92.60)	0.004	HC, NSI > SI ^d
CCL5 (pg/mL)	14,179.42 (452.92)	12,297.84 (1,703.47)	9,823.13 (2,786.36)	< 0.0001	HC > NSI > SI ^d
CCL11 (pg/mL)	429.03 (272.85)	595.64 (183.11)	603.76 (281.21)	0.109	HC = NSI = SI

Data are presented as mean (SD).

^a Body Mass Index; ^b Beck Depression Inventory; ^c Gabriel’s procedure was used for post hoc comparisons; ^d Same results when controlling depression severity as a covariate (MANCOVA).

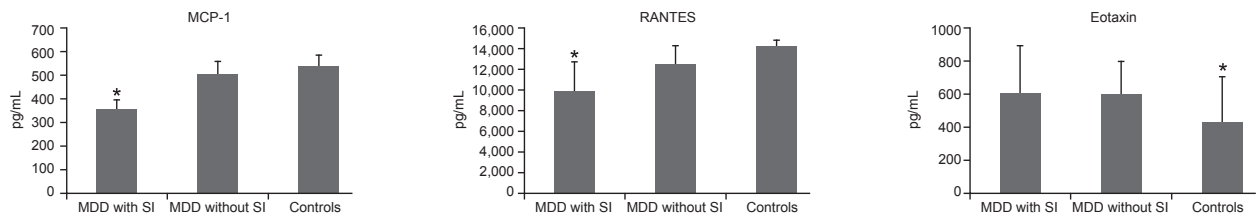


Figure 1 Multivariable analysis of covariance adjusted for age and BMI.

Multivariable analysis of covariance adjusted for age and BMI showed that MDD with SI ($n = 18$) presented lower levels of MCP-1/CCL2 ($M = 354.51$ pg/mL, ± 39.75 ; $F = 2.96$, $p = 0.031$) and RANTES/CCL5 ($M = 9,823.13$ pg/mL, $\pm 2,786.36$; $F = 11.91$, $p < 0.001$) in comparison with MDD without SI ($n = 12$) (MCP-1, $M = 504.08$ pg/mL, ± 50.89 ; RANTES, $M = 12,384.56$ pg/mL, $\pm 1,758.61$) and controls ($n = 16$) (MCP-1, $M = 537.24$ pg/mL, ± 41.52 ; RANTES, $M = 14,179.42$ pg/mL, ± 452.92).

Higher levels of Eotaxin/CCL11 in MDD with SI ($M = 603.76$ pg/mL, ± 281.21) and MDD without SI ($M = 591.92$ pg/mL, ± 191.58) were identified when compared to healthy participants ($M = 429.74$ pg/mL, ± 272.85) ($F = 2.77$; $p = 0.04$). All differences remained significant after adjusting for depression severity.

There were no statistically significant difference between MDD without SI and healthy controls in MCP-1 and RANTES levels. There were no statistically significant differences between MDD with and without SI in Eotaxin levels.

* $p < 0.05$ by Tukey's HSD.

by examining bivariate scatter plots; and the Box's Test of Equality of Covariance Matrices was used to test the null hypothesis, which showed that covariance matrices of dependent variables were equal across all groups ($F = 1.40$; $p = 0.33$).

Discussion

The results of this study indicate the existence of differences in chemokine levels between recurrent MDD and healthy controls. In addition, the presence of SI affected significantly the chemokine profile. MDD with SI presented lower levels of MCP-1/CCL2 and RANTES/CCL5 in comparison with MDD without SI and healthy controls.

Although inflammatory changes have been associated with mood disorders and schizophrenia, results from different studies are frequently inconsistent and heterogeneous.^{14,15,25} Chemokine levels have been an understudied topic in psychiatric disorders. Similarly, possible differences in these mediators between individuals with and without suicidal ideation are also an understudied issue. The few studies regarding inflammatory activity and suicide^{26,27} have divergent results. Comparing MDD individuals with healthy volunteers, Lehto et al.²³ found that MDD was associated with lower levels of chemokines MCP-1/CCL2, MIP-1B, and IL-8/CXCL8. In line with these results, our preliminary findings showed reduced MCP-1/CCL2 levels in severe chronic MDD patients reporting suicidal ideation.

There is some recent evidence that non-suicidal and suicidal patients with MDD may have distinct immunological profiles. It was recently shown that suicidal depression had a Th1/Th2 imbalance with lower interleukin-2 (IL-2).²⁸ Th1-type cytokines tend to produce the proinflammatory responses. Excessive proinflammatory responses can lead to uncontrolled tissue damage, thus a mechanism to counteract this damage is necessary. In excess, Th2 responses will counteract the Th1 mediated microbicidal action. The optimal scenario seem to be that humans should produce a well balanced Th1 and Th2 response, suited to the immune challenge (Berger 2000). These results of our study corroborate the hypothesis of a disruption in Th1/Th2 balance in MDD with suicidal ideation. Low plasma concentrations of MCP-1

and RANTES in MDD patients with suicidal ideation could be an important factor in the pathogenesis of this disorder, as these proteins have either a protective or detrimental role, depending on the inflammatory stimulus, cell type, or disease state.^{29,30} Prior studies have shown that the inhibition of MCP-1 activity, using neutralizing antibodies or in knock-out mice lacking MCP-1, resulted in a dysregulation of the cytokine balance and increased mortality.³¹ In addition, our findings are in line with other report that found activation of inflammatory response in Cerebrospinal Fluid (CSF) of individuals who committed suicide.³²

The results of the present study must be interpreted in light of its limitations. One of them is the small sample size, therefore, this data should be considered preliminary. The participants included in MDD groups were taking antidepressants, and we could not rule out that our results may be due to possible anti-inflammatory effects of such medications on chemokines levels. In addition, the authors did not exclude nicotine users from the sample, which can be an important confounding factor for chemokine analyses. Because only female participants were included, other studies must be conducted including males.

Even considering the limitations, our results demonstrate for the first time that suicidal patients possibly display a distinct chemokine profile compared to non-suicidal depressed patients. If these results were confirmed in future researches, chemokine measurements may potentially be converted into a biomarker for suicidality in individuals with MDD.

Disclosures

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* Modest

** Significant

*** Significant: Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.

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