ORIGINAL ARTICLE

Increased levels of plasma IL-1b and BDNF can predict resistant depression patients

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SUMMARY

BACKGROUND: *There is no strong evidence on the link between inflammatory profile and pattern of drug treatment response in depressive patients that could result in Coronary Artery Disease occurrence.*

OBJECTIVE: *This study aimed to compare the subclinical atherosclerosis markers, inflammatory profile, and BDNF production in Resistant Depression (RD) or Bipolar Affective Disorder (BAD) patients under conventional treatment.*

METHODS: *The population evaluated was comprised of 34 RD, 43 BAD, and 41 controls. Subclinical atherosclerosis markers were evaluated using ultrasonography, tomography, and exercise stress test. Plasma concentrations of TNFα, IL-1β, IL-6, and BDNF were measured using Luminex100™. The usCRP concentration was measured using turbidimetric immunoassay. IL1B, IL6, and TNFA expression were determined using TaqMan®. For the statistical analysis, the significance level was established at p<0.05.*

RESULTS: *Concerning subclinical atherosclerosis markers, only O2 consumption was reduced in the BAD group (p = 0.001). Although no differences were found in gene expression, BDNF and IL-1β plasma concentration was increased in the RD group (p = 0.002 and p = 0.005, respectively) even with an antidepressant treatment, which suggests that these drugs have no effect in IL-1β secretion and that the inflammasome may play a role in therapy response.*

CONCLUSION: *Taken together, both BDNF and IL-1β plasma concentrations could be used to the early identification of RD patients.*

KEYWORDS: *Bipolar Affective Disorder, Depression, Inflammation, Atherosclerosis, BDNF, IL-1β*

INTRODUCTION

Mood disorders have been recognized by the World Health Organization (WHO) as a major public health problem. Depression is a devastating disorder and one of the leading causes of disability worldwide, affecting up to 10% of the adult population [1,2]. Bipolar Affective Disorder (BAD) is a relatively rare affective disorder when compared with unipolar depression, with a lifetime prevalence estimated at 1% to 1.5% of the world population[3].

Clinical and experimental research supports

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a mutual relationship between inflammation and mood disorders. Patients with major depressive disorder and other neuropsychiatric diseases exhibit increased expression of pro-inflammatory cytokines, including interleukin-6 (IL-6), interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and their receptors, and elevated concentrations of C-reactive protein (CRP) [4]. IL-6, TNFα, and CRP are also implicated in BAD, and an increase in their plasma concentration can occur during both mania and depression episodes [5,6]. Also, studies have found reduced circulating BDNF protein concentration during acute phases of BAD, and this reduction is more significant than in a major depressive disorder. Conversely, BDNF expression is upregulated in response to prolonged treatment with anti-depressant drugs [7,8].

Although effective treatments are available, approximately one-third of all patients with mood disorder fail to respond to conventional antidepressant therapies [9]. The response to antidepressants or lithium may be affected due to inflammatory activity before treatment [10,11]. Moreover, the concentration of IL-6 and acute-phase proteins have been shown to be higher in non-responder patients compared to responder patients [10].

Depressive symptoms have received special attention by cardiologists because the high concentrations of inflammatory markers are risk factors to the development of atherosclerosis, an important Coronary Artery Disease (CAD). BDNF is also expressed in atherosclerotic coronary arteries suggesting its possible role in the pathogenesis of CAD. Thus, controlling inflammation in depression syndrome is an important strategy to prevent CAD in these patients [12-14].

This study aimed to compare subclinical atherosclerosis markers, inflammatory profile, and BDNF production between Resistant Depression (RD) and BAD patients under conventional treatment and euthymic controls, as a way of providing indicators of both the risk for cardiovascular diseases and drug treatment response in a Brazilian population.

MATERIALS AND METHODS

Subjects

Seventy-seven individuals were recruited from an Affective and Anxiety Disorders Program, including 34 Resistant Depression (RD) and 43 Bipolar Affective Disorder (BAD) patients diagnosed based on the Structured Clinical Interview for Diagnostic for DSM-IV Axis I Disorders (SCID-I), a standard research tool to identify bipolar disorder, using the validated questionnaire in Portuguese, applied to all patients by at least two experienced clinicians [15].

According to SCID-I, bipolar disorder is defined by several symptoms during the depressive episode such as anhedonia, sadness, hopelessness, insomnia or hypersomnia, loss of appetite, insecurity. That differs from the manic state, which is characterized by agitation, lack of sleep, hyperactivity, and impulsivity. The symptoms experienced in both episodes affect emotion and cognition and may compromise interpersonal relationship, work capacity and cause psychic distress. Resistant depression was defined as the failure of two or more standard antidepressant therapies at adequate dosing and duration to promote response and remission. The aim of antidepressant therapy is symptom remission or the reinstatement of euthymia—often defined as a score ≤7 on the total Hamilton Depression Rating Scale (HDRS) [16]. In our study, the resistant depression group had failed to respond to at least two previous drug treatments.

Forty-one subjects were controls (C). Control participants were euthymic with no previous mood disorder (based on SCID), chronic inflammatory condition or known coronary artery disease or any atherosclerotic vascular disease.

For all groups, individuals of any gender who were in the range of 21 to 70 years old were recruited. To reduce potential additional confounders, we also excluded subjects with other psychiatric diagnosis (depression with response or remission, schizophrenia, personality disorder), patients with known coronary artery disease, any atherosclerotic vascular disease, or any chronic inflammatory disorder or auto-immune disease such as Chrom's colitis, systemic lupus erythematosus, rheumatoid arthritis or other autoimmune or infectious diseases.

This study was approved by the Ethics Committee of Dante Pazzanese Institute of Cardiology, São Paulo and all subjects who agreed to participate in the study signed a written informed consent.

Subclinical atherosclerosis markers

Subclinical atherosclerosis evaluation was based on carotid intima-media thickness (CIMT) obtained with a high-resolution echo-colour-Doppler (Acusson, Model Aspen Advanced or similar) and 10 MHz linear transducer. The search for coronary atherosclerotic plaques was made with ultrafast comput-

ed tomography using the Imatron RC-150 (Imatron Corporation, San Francisco, California). Imaging procedures were characterized by axial heart with 3 mm slice thickness, at the end of diastole electrocardiography-triggered at 100 ms time interval during the inspiratory pause. Furthermore, the quantity or score of coronary calcium was estimated. Myocardial ischemia was diagnosed using the exercise test (ET) per Ellestad protocol [17]. The studied population was asymptomatic and had no previous history of coronary events.

RNA isolation and cDNA synthesis

The whole blood was collected into PAXgene® tubes (QIAGEN, Hilden, Germany) and PAXgene® Blood RNA Kit (QIAGEN, Hilden, Germany) was used to purify the total RNA per manufacturer's instructions. The RNA quantification and integrity were determined by Qubit® 2.0 Fluorometer (Life Technologies, Carlsbad, USA) and Agilent 2200 Tape Station® platform (Agilent Technologies, Santa Clara, USA), respectively. For the cDNA synthesis, 800ng of total RNA and High-Capacity cDNA Reverse Transcription kit (Life Technologies, Carlsbad, USA) were used per manufacturer's instructions.

Quantitative RT-PCR (qPCR)

The mRNA quantification of *IL1B, IL6,* and *TNFA* was performed by qPCR using TaqMan® Gene Expression Assay (Life Technologies, Carlsbad, USA) and RotorGene® platform (QIAGEN, Hilden, Germany). The GAPDH gene was chosen as an endogenous reference using GeNorm (qbase+, Biogazelle). The PCR was performed in a multiplex format using Quantifast® Multiplex PCR assay (QIAGEN, Hilden, Germany). Thus, target genes and GAPDH were labeled with fluorescent dye FAM and VIC, respectively. Data were analyzed using Rotor-Gene® Q - Pure detection software (QIAGEN, Hilden, Germany). The results were obtained by relative quantification method ($2^{-\Delta\Delta Ct}$) [18].

Protein measurements

TNFα, IL-1β, IL-6 and BDNF concentrations in EDTA plasma were measured by multiplex assay using Luminex 100™ system (Luminex Corporation Austin, EUA) and custom Milliplex Map Kits (EMD Millipore Corporation, Billerica, USA), following the manufacturer's instructions. The data were analyzed using Xponent 3.1 software. The usPCR concentration was measured by an automated turbidimetric immunoassay using Hitachi 912 Chemistry Analyzer (Myco Instrumentation, Renton, WA).

Statistical analysis

The results were analyzed using SPSS 16 (SPSS Inc., Chicago, IL, USA) and the significance level was established at $p<0.05$. Through the Kolmogorov-Smirnov test, it was verified that variables did not follow a normal distribution. For non-parametric data, the Kruskal-Wallis test was performed, and data are presented as median and interquartile. Multiple comparison analysis was performed to identify differences between groups. To compare the frequencies of qualitative variables, chi-square test ($\chi 2$) or Fisher's exact were performed. Spearman Correlation Coefficient was used to examine the relationship between gene expressions and protein measurements with time since diagnosis and subclinical atherosclerosis markers. Multiple logistic regression analysis was used with BMI as a confounder variable.

RESULTS

In table 1, the demographic characteristics from controls, RD, and BAD groups are shown. There were no differences in gender, ethnicity, Body Mass Index (BMI), and age. When subclinical atherosclerosis markers were evaluated, only the O2 consumption was reduced in the BAD group (table 1). Regarding drugs, the RD group was taking significantly more antidepressants and the BAD group antipsychotics. When we fragmented the class of antidepressants and compared patients under SSRIs treatment between all 3 groups, we observed a p-value of 0.000. This difference may be related to the controls that were not under drug treatment compared to both patient groups. However, when we compared only both patient groups (RD and BAD), this significance disappeared.

Although molecular analysis showed that *IL1B, IL6* and *TNFA* expression were not different between the groups (data not shown), BDNF and IL-1β plasma concentrations showed a statistical difference (table 2). After multiple comparison analysis, BDNF plasma concentrations were increased in both the RD and BAD groups compared with control subjects, while IL-1β plasma concentration was higher in the RD group than in the controls (figure 1 A and B).

Since obesity commonly occurs with depression

and is associated with inflammatory processes, it may act as a confounder variable. So, after controlling for BMI, using regression analysis, BDNF concentrations of the RD and BAD groups were 88% and 42% more than the controls, respectively, but remained significant only in the RD group. IL-1β concentrations were different only between the RD and the controls (p = 0.007). When controlled for BMI, logistic regression showed that the RD and BAD groups were 1.79 and 0.84 times more likely to be IL-1β positive than controls, but were only significant in the RD group (figure 1 C and D). We found a positive correlation of time since diagnosis with BDNF (Spearman's rho = 0.336, p = 0.001) and IL-1β (Spearman's rho = 0.299, p = 0.003) (data not shown) and a negative correlation between BDNF with right CIMT (Spearman's rho = -0.371, p = 0.022) and left CIMT (Spearman's rho = -0.375, p = 0.020) in Control group (data not shown).

DISCUSSION

Heart diseases and depression are two of the major illnesses worldwide and seem to co-occur in a bi-directional way. However, there is still an unknown complex physiologic mechanism to explain both conditions. When we evaluated subclinical atherosclerosis markers, the BAD group showed less O2 consumption in the cardiac stress test. This could be due to the side effects of BAD drug therapies, that are fre-

TABLE 1. DEMOGRAPHIC CHARACTERISTICS AND SUBCLINICAL ATHEROSCLEROSIS MARKERS OF THE CONTROL, RD AND BAD GROUPS

	C	RD	BAD	p
Gender				
Female	33 (33)	29 (29)	38 (38)	0.600*
Male	8 (44.4)	5 (27.8)	5 (27.8)	
Ethnicity				
White	20 (31.7)	19 (30.2)	24 (38.1)	0.908*
Brown	14 (40.0)	9 (25.7)	12 (34.3)	
Black	6 (40.0)	5 (33.3)	4 (26.7)	
Asian	1 (25.0)	1 (25.0)	2 (50.0)	
Others	0 (0)	0 (0)	1 (100)	
Age (years)	50.4 ± 9.0	50.5 ± 12.0	46.5 ± 10.6	0.157**
BMI (kg/m^2)	28.7 ± 8.4	30 ± 6.9	29.4 ± 4.9	0.259**
WC (cm)	61.3 ± 43.5	99.3 ± 13.0	83.5 ± 34.0	0.005**
CIMT				
Right (mm)	0.71 ± 0.19	0.66 ± 0.18	0.62 ± 0.22	0.272**
Left (mm)	0.69 ± 0.16	0.66 ±0.17	0.6 ± 0.20	0.206**
Ankle Brachial Index				
Right	0.92 ± 0.09	0.93 ± 0.14	0.94 ± 0.07	0.195**
Left	0.89 ± 0.09	0.86 ± 0.19	0.91 ± 0.10	0.647**
Tomography				
Calcium score	17.9 ± 84.7	34.9 ± 148.8	9.36 ±46.5	0.309**
Cardiac Stress test				
Effective (%)	40.5	27.4	32.1	0.499*
Ineffective (%)	25	41.7	33.3	
O2 consumption (TEM)	11.0 ± 3.2	10.9 ±7.3	8.3 ±2.0	0.001**
Framingham score (Directive 2007)	1.88 ± 2.6	2.35 ± 3.7	1.48 ± 3.3	0.367**

Values are shown as mean (%); mean ± SD for age, BMI, WC, Right and Left CIMT, Ankle Brachial Index Right and Left, and Calcium score; and mean (%) for Cardiac Stress test, Effective and Ineffective; C - Controls; RD - Resistant Depression; BAD - Bipolar Affective Disorder; BMI - Body Mass Index; WC - Waist Circumference; CIMT - Carotid intima-media thickness. *Chi-square test; **Kruskal-Wallis Test.

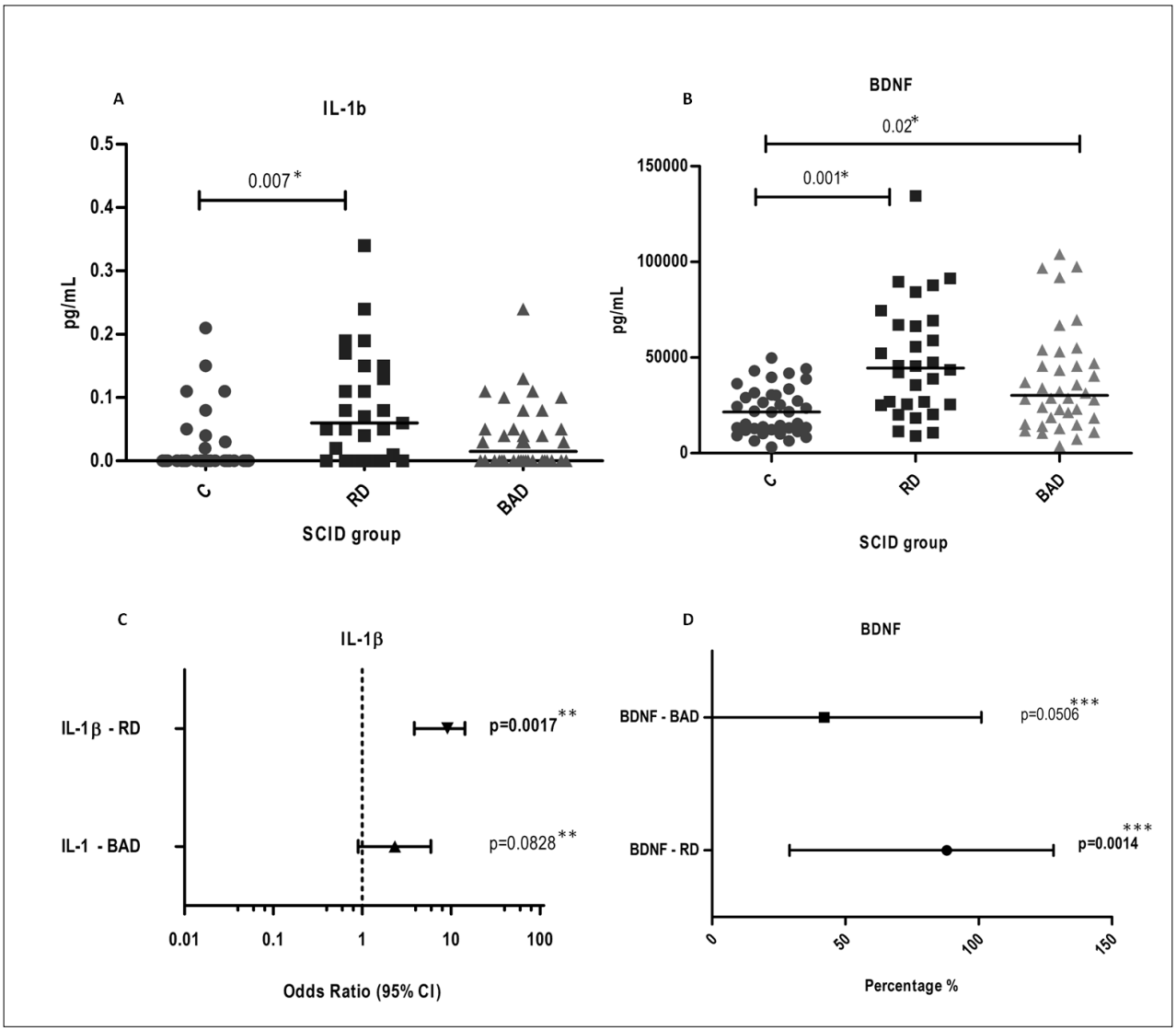

FIGURE 1. A AND B: MULTIPLE COMPARISON ANALYSIS OF IL-1B AND BDNF PLASMA CONCENTRATION BETWEEN CONTROLS (C), RESISTANT DEPRESSION (RD) AND BIPOLAR AFFECTIVE DISORDER (BAD) GROUPS; C AND D: MULTIPLE LOGISTIC REGRESSION FOR BMI VARIABLE ASSOCIATED WITH IL-1B AND BDNF PLASMA CONCENTRATION. * MULTIPLE COMPARISON ANALYSIS; ** LOGISTIC REGRESSION; ***GENERALIZED GAMMA MODEL.

quently associated with weight gain and metabolic disturbance [19]. However, the remaining parameters were not different between groups.

Since atherosclerosis is a slow and progressive disease, it was observed that 30.9% of the patients had the disease for less than five years when they participated in the study, the time between the diagnosis of mood disorder and laboratory testing was not sufficient to observe the association between depression symptoms and CAD. However, a study observed that patients with slow coronary flow have higher rates of depression, anxiety, and overall psychological distress. So, slow-coronary-flow patients should have special medical monitoring [20].

Besides that, our patients have been polymedicated so far, which might explain the lack of association of patients groups with atherosclerosis markers. One of the medications used by our patients was Selective Serotonin Reuptake Inhibitors (SSRI), a widely used antidepressant that is also associated with a lower risk of death or recurrence of myocardial infarction [21]. A similar result was found for coronary heart disease. The authors have confirmed that inflammation and metabolic factors are significantly increased in depression and suggest a higher risk of coronary heart disease. Using SSRI may reduce these factors and, consequently, the risk of coronary heart disease, as suggested in a previous study [22]. Inflammation underlies both heart diseases and depression, so inflammatory markers seem to be elevated in both conditions [23].

We found that BDNF is significantly higher in RD and BAD patients than in controls. It is known that BDNF blood concentrations are associated with clinical changes in depression [24]. However, regarding the cause and effect relationship, Molendijk and colleagues showed in a longitudinal study that the decrease in plasma BDNF concentration is a peripheral manifestation of depression[25].

Since our patients were under drug treatment, mainly antidepressants (data not shown), the high concentrations of BDNF found in both RD and BAD groups were expected, suggesting a positive pharmacotherapy response. However, there is no consensus about the effect of antidepressant treatment on BDNF changes. Bus and colleagues (2014) found that persistent and remitted major depressive disorder patients presented a decline in BDNF levels, which were not influenced by antidepressants [26]. On the other hand, low BDNF concentrations have been associated with major depressive disorders and found to normalize with antidepressant treatment [27]. The same results were observed by Castren in 2016 [28]. A recent meta-analysis shows that a period of treatment with conventional antidepressants leads to the increase of BDNF concentration[29], making this molecule an essential determinant of antidepressant efficacy. However, in these studies, the follow-up period was 2 years or less. In our study, RD and BAD patients had used antidepressants for more than 2 years, 74.3% and 73.8%, respectively. Also, 60% of RD patients and 50% of BAD patients had been using antidepressant drugs for more than five years.

Although some researchers suggest BDNF as a biomarker for major depressive and bipolar disorders [25,30], when controlled for the confounding variable of BMI, only the RD group remained significantly associated with BDNF.

When we analyzed BDNF with subclinical atherosclerosis markers between groups, we found a significant negative correlation between BDNF with right/left CIMT only in the control group. These results were not found in both disease groups (table 6). Hatch and colleagues showed that lower BDNF was associated with higher mean CIMT in adolescents with symptomatic Bipolar Disorder [31]. However, our patients were under medication treatment which may have led to an increase in BDNF concentrations and consequently prevented carotid intima-media thickening. This could explain the lack of association between subclinical atherosclerosis markers and the study groups (table 2).

In addition to BDNF measurement, we also evaluated gene expression and plasma concentration of IL-1β, IL-6 and TNF-α, which are the most important biomarkers of an inflammatory condition in depression, according to literature [4,32]. In this study, only IL-1β concentrations were significantly higher in refractory depression patients than controls. Even after controlling BMI as a confounding variable, the RD group remained significantly associated with IL-1β. In 2012, a meta-analysis showed that only in the European studies the IL-1β concentrations were significantly higher in patients with major depressive disorder [33].

In depression syndrome, some studies showed a role of IL-1β in mediating BDNF decrease [4,27] This means that when there is an increase of IL-1β concentrations, a reduction in BDNF concentrations occurs [27]. According to literature, in patients undergoing antidepressant treatment, there is a decrease of IL-1β and an increase of BDNF concentrations. In our study, the results did not show this profile. Although BDNF concentrations were increased in RD patients undergoing treatment, IL-1β concentrations remained high in this group.

A meta-analysis study including 6 publications showed that antidepressant treatments reduce IL-1β concentrations [34]. Our results, however, showed a different profile that is consistent with many clinical studies and *in vitro* assays. Hernandéz et al (2008) studied patients with major depressive disorder undergoing treatment with SSRI for 52 weeks and found an 86% increase in IL-1β concentrations between 0

TABLE 2. BDNF, IL-1B, IL-6 AND TNFA CONCENTRATIONS IN CONTROL, RD AND BAD GROUPS

Protein	C	RD	BAD	p*
BDNF (pg/mL)	21793 (12613; 32555.5)	43642 (25612; 66384)	32333 (19989; 53524)	0.002
IL-1β (pg/mL)	0.00 (0.00; 0.03)	0.05 (0.00; 0.14)	0.02 (0.00; 0.05)	0.005
IL-6 (pg/mL)	0.41 (0.10; 0.93)	0.26 (0.14; 0.89)	0.38 (0.12; 1.43)	0.731
TNFα (pg/mL)	6.15 (3.96; 10.20)	5.69 (3.93; 7.92)	6.87 (5.19; 9.26)	0.244
usCRP (mg/dL)	0.60 (0.22; 0.90)	0.60 (0.14; 1.00)	0.60 (0.26; 0.95)	0.813

Values are shown as median (25%; 75%); C - Controls; RD - Resistant Depression; BAD - Bipolar Affective Disorder; BDNF - Brain-derived neurotrophic factor; IL1-β - Interleukin-1beta; IL-6 - Interleukin-6; TNFα - Tumor necrosis factor-alpha; usCRP - ultrasensitive C-reactive protein. *Kruskal-Wallis Test.

and 52 weeks [35]. Also, an *in vitro* study that evaluated the effect of three antidepressant drugs on cytokine secretion showed that Citalopram and Mirtazapine increase IL-1β secretion [36]. This suggests that different types of antidepressants can lead to a variation in IL-1β secretion, probably due to the mechanism of action of the drug [37].

According to literature, IL-1β production may affect the neuronal plasticity through impairing the signaling triggered by the binding of BDNF to TrkB receptor [38,39]. Therefore, the results may suggest that in patients with resistant depression, despite the high production of BDNF in response to drug treatment, there is also an increased production of IL-1β that could interfere with BDNF effect. *IL1B* was not expressed differently between the groups; however, the elevated IL-1β secretion in the RD group leads us to expect that inflammasome complexes are an individual characteristic which may play an important role in the antidepressant drug resistance.

In 2013, Iwata proposed the "inflammasome hypothesis of depression" [40]. It was based on the pathway between NLRP3 to IL-1β. NLRP3 is a cytosolic protein complex, also known as inflammasome. Usually, this complex is formed in response to infection caused by pathogenic and non-pathogenic microorganisms. Inflammasome proteins recognize these microorganisms, activate caspase-1, which cleaves the pro- IL-1β in secreted cytokine [4,41].

Alcocer-Gómez et al. (2014) have shown that IL-1β concentrations, NLRP3, and caspase-1 gene expression were increased in non-treated major depressive disorder patients and were reduced in patients who receive amitriptyline [42]. This study is in agreement with the inflammasome hypothesis of depression, which states that psychological stress activates NLRP3 and leads to the development of depression [40].

In our study, the patients were diagnosed with refractory depression because they did not respond to previous antidepressant treatment. About 29% to 46% of patients with depression do not adequately respond to the first antidepressant treatment, and between 19% and 34% of these patients were considered as non-responders [43,44].

Our results showed that BDNF and IL-1β concentrations were increased in RD patients, but there was no difference in gene expression in this group compared to others. This evidence suggests that, in Refractory Depression, the antidepressant drugs acted on mRNA transcription but had no effect on the secretion mechanism of IL-1β. Given the role of the inflammasome in depression, our results lead us to suppose that refractory depression patients have a different cleavage mechanism to secret IL-1β. Also, a positive correlation was also found between IL-1β, BNDF and time of diagnosis that highlight our hypothesis. However, more studies are necessary to validate it.

Many studies have discussed the use of both anti-inflammatory and antidepressants drugs in RD treatment. However, there is still a concern about the adverse events of anti-inflammatory drugs and the interaction between these drugs and antidepressants [45].

CONCLUSION

In conclusion, our results suggest that when taken together, both BDNF and IL-1β plasma concentrations could be used in the early identification of RD patients, allowing a pharmacotherapy association with anti-inflammatory drugs, for example. However, further studies are necessary in order to validate these findings.

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RESUMO

FUNDAMENTAÇÃO: *Não há fortes evidências sobre a associação entre o perfil inflamatório e o padrão de resposta ao tratamento medicamentoso em pacientes depressivos que podem resultar em ocorrência de doença coronariana.*

OBJETIVO: *O objetivo deste estudo foi comparar os marcadores de aterosclerose subclínica, o perfil inflamatório e a produção de BDNF em pacientes com Depressão Resistente (DR) ou Transtorno Afetivo Bipolar (BAD) sob tratamento convencional.*

MÉTODOS: *A população avaliada incluiu 34 RD, 43 BAD e 41 controles. Os marcadores de aterosclerose subclínica foram avaliados por ultrassonografia, tomografia e teste de esforço. As concentrações plasmáticas de TNFα, IL-1β, IL-6 e BDNF foram medidas utilizando*

Luminex100TM. A concentração de usCRP foi medida por imunoensaio turbidimétrico. A expressão de IL1B, IL6 e TNFA foi determinada usando TaqMan®. Para as análises estatísticas, foi estabelecido o nível de significância de p < 0,05.

RESULTADOS: *Quanto aos marcadores de aterosclerose subclínica, apenas o consumo de O2 foi reduzido no grupo BAD (p = 0,001). Embora não tenham sido encontradas diferenças na expressão gênica, a concentração plasmática de BDNF e IL-1β foi aumentada no grupo RD (p = 0,002 e p = 0,005, respectivamente) mesmo sob tratamento antidepressivo, o que sugere que esses medicamentos não têm efeito na secreção de IL-1β e que o inflamassomo pode desempenhar um papel na resposta terapêutica.*

CONCLUSÃO: *Juntas, as concentrações BDNF e IL-1β poderiam ser usadas para a identificação precoce de pacientes com DR.*

PALAVRAS-CHAVE: *Transtorno afetivo bipolar. Depressão. Inflamação. Aterosclerose. BDNF, IL-1β.*

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