# Inflammation and Neurodegeneration in Patients with Early-Stage and Chronic Bipolar Disorder



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**SUMMARY**

**Objective:** The increase in the circulatory cytokine levels observed in patients with bipolar disorder (BD) may imply involvement of inflammation in the pathogenesis of mood disorders. However, the association between the inflammatory process and the stage and severity of illness is not well understood. In this study, our aim was to investigate the association between neuroinflammation and disease progression in the clinical course of BD.

**Method:** IL-6, TNF-α, IL-1 receptor antagonist (IL-1RA), neuron- specific enolase (NSE) and S100B were measured by ELISA in plasma samples of patients at early-stage BD (n=30), chronic BD (n=77) and healthy controls (n=30).

**Results:** Chronic BD patients showed significantly increased levels of all measured inflammatory markers as compared to early-stage BD patients and the healthy controls. IL-6 and IL-1RA levels correlated with NSE and/or S100B levels and TNF-α levels correlated with Montgomery-Asberg Depression Rating Scale scores and Clinical Global Impression Scale scores.

**Conclusion:** Our results indicate that inflammation appears to be particularly associated with IL-1RA and IL-6 activity, progressing at later stages of BD and possibly associated with gliosis and neuronal loss.

**Keywords:** Bipolar disorder. inflammatory cytokines, neuron-specific enolase, S100B, neuroinflammation

## INTRODUCTION

Bipolar disorder (BD) is one of the major causes of mortality and morbidity in the general population (Fagiolini et al. 2013). Aetiology and pathophysiology of the disease have still not been well understood despite extensive accumulated knowledge on the epidemiology, symptoms and complications of BD, (Rosenblat et al. 2014).

Even though Wagner-Jauregg suggested the association of inflammation with psychosis in 1887, hypotheses on the role of inflammation have been developed after clarification of the role of lithium on the immune system (Wagner-Jauregg 1887, Horrobin and Lieb 1981). Findings on the interaction of the immune system and the central nervous system in BD brought new perspectives on the pathogenesis of mood disorders (Rosenblat and McIntyre 2016, Rosenblat and McIntyre 2017). Moreover, demonstration of polymorphisms in inflammation-related and neuroprotective genes and alterations of peripheral markers of inflammation represent one of the turning points in the field of mood disorders. The most notable of these alterations include increased circulatory levels of inflammatory cytokines such as IL-1, IL-6 and TNF-α, acute phase proteins and vascular adhesion molecules. These changes might be effective on the neurotransmitter synthesis production, neuroplasticity and

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the cognitive functions in patients with BD (Berk et al. 2011, Stertz et al. 2013, Munkholm et al. 2013a).

Nevertheless, time dependent alterations of immunological factors and their temporal association with progression of gliosis and neuronal death have not been adequately explained. There are many studies on the physical properties, function, and expression of the S100 protein family which is one of calcium-binding groups of proteins (Donato et al. 2003). In the central nervous system S100B, one member of the S100 family, has drawn attention in glioblastoma. It regulates cell shape, energy metabolism, contraction, cell-to-cell communication, intracellular signal transduction, and cell growth (Schroeter et al. 2013). S100B is located in the cytoplasm and can be actively released by some particular cells including astrocytes and oligodendrocytes (Steiner et al. 2007). Effects of extracellular S100B depend on its concentration. In nanomolar concentrations, it stimulates the growth and differentiation of neurons and astrocytes, and reduces stress-induced damage, whereas in micromolar concentrations, it has a negative effect, stimulating neuronal apoptosis, production of proinflammatory factors, and release of TNF-α by microglial cells (Donato et al. 2009, Rajewska-Rager and Pawlaczyk 2016, Schmitt et al. 2007). S100B elevation has been associated with post-traumatic brain damage, dementia (Alzheimer type and Down syndrome associated) and progressive neurodegeneration associated with AIDS (Fano et al. 1995).

Neuron specific enolase (NSE) is one of the glycolytic enzymes located in the cytoplasm of neurons and is not actively secreted (Kaiser et al. 1989). Thus it has been regarded as a biomarker for neuronal injury (Schroeter et al. 2011). NSE levels were shown to be elevated in epilepsy, Creutzfeldt-Jakob disease, and traumatic brain injury (Moritz et al. 2010). In this context, it is not entirely understood whether BD patients have an inherent defect in cytokine production (e.g. have high cytokine levels before disease onset) or cytokine level changes emerge as an unavoidable side effect of disease processes (e.g. gliosis). The validity of cytokine levels as a biomarker of disease progression, neuronal death and cognitive decline in BD has also not been adequately investigated.

In this study the hypothesis that immunological factors are effective on the pathogenesis of BD, that their levels increase with the progress of BD and that they are realted with neurodegenerative biomarkers. It has been aimed to measure plasma levels of major inflammatory cytokines IL-6 and TNF-α, IL-1 receptor antagonist (IL-1RA), the natural inhibitor of inflammation, and markers of neuronal death (NSE) and gliosis (S100B), and investigate their correlation with the clinical variables of BD including duration of illness, severity of depressive and manic episodes, clinical functionality and severity of psychotic symptoms and also their relationship with mood episodes. These analyses, carried out in early-stage and chronic BD patients, have evaluated whether the changes in cytokine levels are the outcomes of inherited immune system disorders or of pathological mechanisms coming into effect with the disease process.

## METHODS

### Participants

A total of 77 consecutive chronic BD patients, 30 consecutive first episode (early stage) BD patients (within the first three years from the onset of manic episode without a preceding depressive episode) and 30 age and gender matched healthy controls were included in the study.

Inclusion criteria for the early stage patient group was a history of only single manic episode. Patients with depressive symptoms (including inpatient treatment) were excluded. BD patients were diagnosed in accordance with Diagnostic and Statistical Manual (DSM)-IV-TR criteria and the investigation was carried out according to the principles expressed in the Declaration of Helsinki (American Psychiatry Association,1994). Healthy controls were recruited from the same areas as the patients and assessed by the structured clinical interview for DSM-IV Axis 1 disorders to eliminate history of psychiatric illness and treatment and clinical interview; mental retardation was an exclusion criteria. Study exclusion criteria for the patients comprised any history of substance abuse, mental retardation, any other psychiatric or medical disorder, immunomodulating or immunosuppressant drug use, pregnancy or breast feeding, dementia, epilepsy, cranial trauma, and immunization in the last 12 months. Study exclusion criteria for the healthy controls were having any chronic disease, history of immunomodulating or immunosuppressant drug use, pregnancy or breast feeding, antidepressant drug use within the last 1 year and mental retardation. All patients were assessed by Young Mania Rating Scale (YMRS), Montgomery-Asberg Depression Rating Scale (MADRS), Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI) Scale.

This study were approved by Istanbul Medicine Faculty ethics committee and supported by Istanbul University Research Project Department (project number:57877). Informed written consent was obtained from all patients and healthy controls.

## ELISA

Blood was obtained between the times of 13.00 and 14.00 from the forearm of all patients. Plasma was extracted from blood samples and kept at –80°C until analyses. ELISA kits were used for detection of plasma levels of TNF-α, IL-6 [Diaclone (Besancon, France)], IL-1RA, S100B and NSE (YH Biosearch Laboratory- Shanghai, China), as per the

manufacturer's instructions. With the ELISA kits used, the minimum detectable levels of NSE, IL-1RA, S100B, TNF-α and IL-6, were respectively, 0.05 ng/ml, 0.1pg/ml, 0.1pg/ml, 8 pg/ml and 2pg/ml.

### Statistical Analysis

Statistical analysis was performed by GraphPad Prism 6 program. Using the Kolmogorov-Smirnov test, most of the parameters were found not to have a normal distribution. Therefore, differences between study groups were examined by the Kruskal-Wallis test. Dunn's multiple comparisons test was used for post-hoc analysis. Two group comparisons were done with the Mann-Whitney U-Test. Independent variables were examined with the chi-square test or Fisher's exact test, as required. Correlation analyses between cytokine, NSE, S100B and sociodemographic and clinical variables were performed with Spearman's correlation test. The p value < 0.05 was accepted to be statistically significant.

## RESULTS

### Clinical and Demographic Features

The sociodemographic characteristics of the study sample are presented in Table 1. The Early stage (first episode) BD patients were inadvertently younger than the chronic BD patients. Hence, healthy controls had been selected from a broad age range to match the ages of both of the BD patient groups. Although age values of the study groups were found to be significantly different by Kruskal-Wallis, Dunn's test did not give significant difference between healthy controls as compared to the chronic or the first episode BD groups. The mean ages at disease onset were 23.9 (±8.7) years in chronic group and 22.8 (±5.1) years in early-stage group. In the chronic BD group 94.8% (n=73) of patients were on antiepileptic mood stabilizer medication 46.7% (n=36) on valproic acid, 29.8% (n=23) on lithium, 10.3% (n=8) on antiepileptic combination, 6.4% (n=5) on carbamazepine, 1.4% (n=1) on both topiramate and lamotrigine were found out. Antipsychotic medication was used by 82.1% (n=60) of the patients and 2.8% (n=2) of the patients were on antidepressive medication In the early stage group, 60% (n=18) of the patients were on medication; 53% (n=16) were on antiepileptic mood stabilizer and 40% (n=12) were using antipsychotics. Patients were divided into five groups on the basis of mood episodes as the euthymic (without symptoms meeting the mood episode criteria within the previous 2 months), depressive, hypomanic, manic and mixed episode. In the early stage BD group, 43% (n=13) of patients were in the manic, 40% (n=12) were in the euthymic, 7% (n=2) were in the depressive, 7% (n=2) were in the hypomanic and

**Table 1.** Sociodemographic Data of the Study Sample

| | | Early-stage BD (n=30) | Chronic BD (n=77) | Healthy Controls (n=30) | P value |
|---|---|---|---|---|---|
| Age (mean ± SD) | | 25.27±6 | 37.81±11.9 | 31.7±11.8 | <0.001 |
| Sex | | | | | |
| Female | | 23 (76.6%) | 33 (42.8%) | 13 (43.3%) | 0.148 |
| Male | | 7 (23.4%) | 44 (57.2%) | 17 (56.7%) | |
| Education (years) | | 12.3 ± 3.8 | 10.9±3.7 | 16.7±3.6 | <0.001 |
| Onset of disease (years) | | 22.8 ± 5.1 | 23.97 ± 8.7 | | 0.196 |
| Mood during blood sampling | Euthymic | 12 (40%) | 50 (65%) | | 0.063 |
| | Manic | 13 (43%) | 20 (26%) | | |
| | Depressive | 2 (7%) | 7 (9%) | | |
| | Hypomanic | 2 (7%) | 0 (0%) | | |
| | Mixed | 1 (3%) | 0 (0%) | | |
| Psychosis | Psychotic | 11 (36%) | 19 (24%) | | 0.237 |
| | Nonpsychotic | 19 (64%) | 58 (76%) | | |
| Duration of disease (months) | | 29.7 ± 34.9 | 167.3 ± 124.7 | | <0.001 |
| PANSS-positive (mean ± SD) | | 19.4 ± 12.9 | 11.4± 7.2 | | 0.002 |
| CGI (mean ± SD) | | 3.8 ± 2.3 | 2.8 ± 2.1 | | <0.001 |
| MADRS (mean ± SD) | | 10.8 ± 10.1 | 7.3 ± 8.7 | | 0.046 |
| YMRS (mean ± SD) | | 20.4 ± 18.7 | 8.8 ± 13.1 | | 0.002 |

BD: bipolar disorder, SD: standard deviation, YMRS: Young Mania Rating Scale, MADRS: Montgomery-Asberg Depression Rating Scale, PANSS: Positive and Negative Syndrome Scale, Clinical Global Impression Scale: CGI.

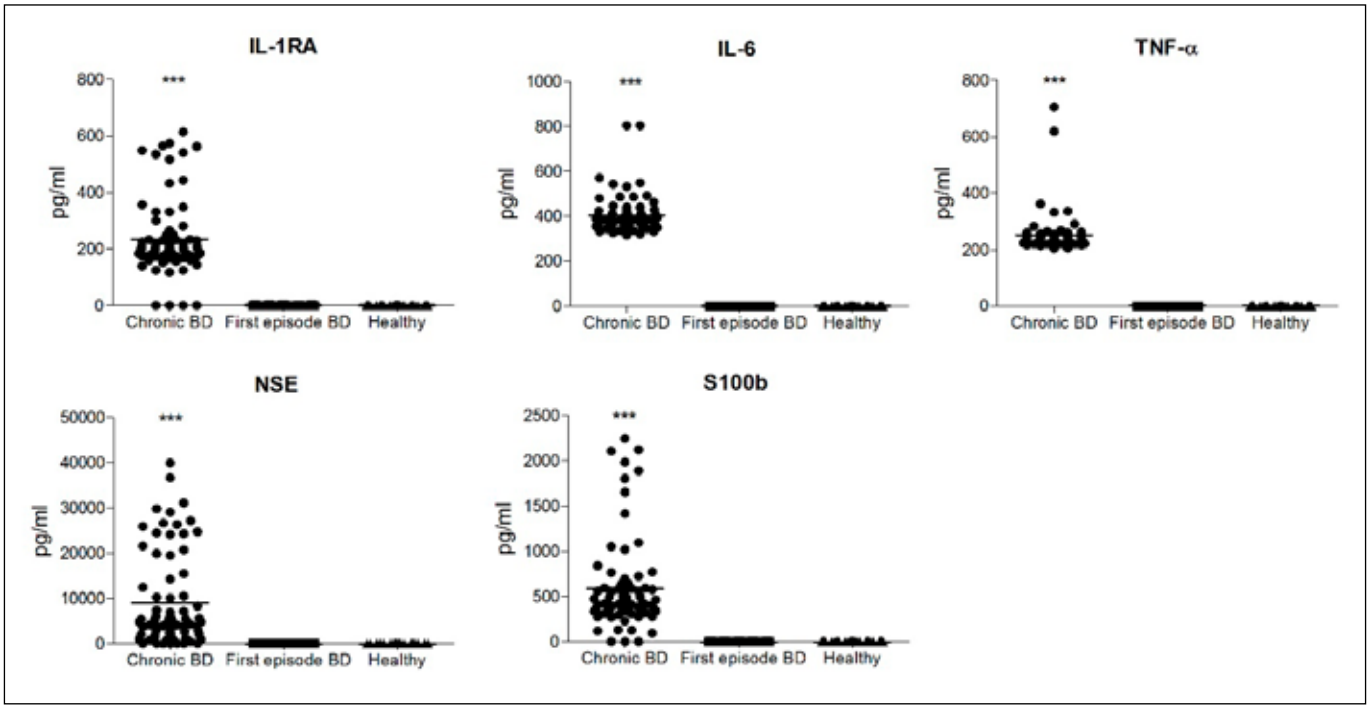


**Figure 1.** Plasma levels of IL-1 receptor antagonist (IL-1RA), IL-6, TNF-α, neuron-specific enolase (NSE), and S100B in patients with chronic bipolar disorder (BD), early-stage BD, and healthy controls. Vertical lines indicate mean values for each group. ***, p<0.001 using Kruskal-Wallis analysis.

3% were in the mixed episode. In the chronic BD group, 65% (n=50) of patients were euthymic, 26% (n=20) were manic, 9% (n=7) were depressive. There were no statistically significant differences between the chronic and early stage first BD groups in terms of mood states at the time of blood sampling. Prevalence of psychotic symptoms was comparable among early stage and chronic BD groups. The mean disease duration was significantly higher in the chronic BD group, as expected. The PANNS, CGI, MADRS and YMRS scores were all significantly higher in early stage patients as compared to chronic patients.

### Cytokine, S100B and NSE Measurements

TNF-α, IL-1RA, IL-6, NSE and S100B levels of the chronic BD patients were significantly higher than those of the early stage BD patients and the healthy controls (all p<0.001 by Kruskal-Wallis). Dunn's post-hoc analysis also showed significantly higher levels (p<0.001 for all comparisons), when the chronic BD patients were compared with the early stage BD patients and the healthy controls. There were no significant differences between the early stage BD patients and the healthy control patients in terms of plasma IL-1RA (p>0.999), IL-6 (p>0.999), NSE (p>0.999), S100B (p=0.880), and TNF-α (p=0.250) levels (Figure 1).

### Correlations and Subgroup Analyses

There were no statistically significant correlations between the chronic BD patients, the early stage patients and the healthy controls with respect to age and plasma IL-1RA, IL-6, NSE, S100B and TNF-α levels (p>0.1 and r correlation coefficient <0.2 for all analyses). There were no significant correlations between previous neuroinflammatuar biomarkers in the chronic and early BD patient groups and illness duration (p>0.1 and r correlation coefficient<0.3 for all analyses). In the chronic BD group, statistically significant direct correlation could be found only between TNF-α levels and MADRS scores. TNF-α levels also showed significant direct correlation in the early stage BD group with CGI scores. Moreover, in the chronic BD group, NSE levels showed trends towards showing an inverse correlation with the PANSS scores (Table 2). In both the chronic and the early BD groups, IL-6 levels showed significant direct correlation with NSE levels. Only in the chronic BD group were the S100B levels moderately correlated with IL-1RA and IL-6 levels (Table 2).

To see the impact of mood during blood sampling on cytokine, NSE and S100B levels, chronic bipolar disorder patients were divided into three groups as the euthymic (n=50), manic (20) and depressive (7) cases and the measured biological parameters were compared among these three groups. No significant difference was found between groups in terms of TNF-α, IL-1RA, IL-6, NSE and S100B levels (p>0.05 for all, data not shown). Likewise, there were no significant differences between patients with and without psychotic features in the chronic and the early stage BD groups in terms of the investigated parameters (Table 3).

**Table 2.**Correlation Analysis Between Cytokine, NSE, S100B Levels and Clinical Variables

| **Chronic BD** | **IL-1RA p(r)** | **IL-6 p(r)** | **TNF-α p(r)** | **NSE p(r)** | **S100B p(r)** |
|---|---|---|---|---|---|
| Duration of Disease | 0.638(0.055) | 0.114(0.184) | 0.816(0.027) | 0.968(0.005) | 0.186(0.152) |
| PANSS | 0.978(0.003) | 0.328(0.115) | 0.799(0.030) | 0.050(-0.224) | 0.330(-0.113) |
| CGI | 0.336(-0.111) | 0.156(0.165) | 0.688(0.046) | 0.148(-0.167) | 0.362(-0.105) |
| MADRS | 0.680(-0.048) | 0.884(-0.017) | 0.024(0.258) | 0.398(-0.098) | 0.368(-0.104) |
| YMRS | 0.954(0.007) | 0.070(0.210) | 0.657(-0.051) | 0.145(-0.168) | 0.411(-0.095) |
| NSE | 0.501 (0.078) | <0.001 (0.429) | 0.312 (0.117) | - | - |
| S100B | 0.017 (0.272) | 0.016 (0.278) | 0.572 (0.065) | - | - |
| **Early Stage BD** | | | | | |
| Duration of Disease | 0.277(-0.209) | 0.492(0.131) | 0.197(-0.247) | 0.144(0.294) | 0.506(-0.126) |
| PANSS | 0.486(0.135) | 0.693(-0.075) | 0.050(0.244) | 0.631(-0.099) | 0.403(-0.159) |
| CGI | 0.165(0.265) | 0.648(-0.087) | 0.019 (0.367) | 0.931(-0.018) | 0.550(-0.114) |
| MADRS | 0.618(0.097) | 0.335(-0.182) | 0.152(0.432) | 0.069(0.362) | 0.909(-0.022) |
| YMRS | 0.427(0.153) | 0.788(-0.051) | 0.816(0.273) | 0.609(-0.105) | 0.825(-0.042) |
| NSE | 0.923 (-0.020) | 0.047 (0.393) | 0.120 (0.319) | - | - |
| S100B | 0.872 (0.031) | 0.297 (0.197) | 0.922 (-0.019) | - | - |

BD: bipolar disorder, YMRS: Young Mania Rating Scale, MADRS: Montgomery-Asberg Depression Rating Scale, PANSS: Positive and Negative Syndrome Scale, CGI: Clinical Global Impression Scale, NSE: neuron-specific enolase.
Significant correlations are denoted with bold characters.

**Table 3.** Comparison of Patients with and without Psychotic Features in Chronic and Early- Stage Bipolar Disorder (BD) Groups

| | **Psychotic** | **Non-psychotic** | **p value** |
|---|---|---|---|
| Early-stage BD | | | |
| IL-1RA | 1.2±1.2 | 0.7±0.8 | 0.123 |
| IL-6 | 0.1±0.0 | 0.1±0.0 | 0.417 |
| NSE | 1.8±0.7 | 1.5±0.6 | 0.194 |
| S100B | 1.2±0.6 | 1.3±0.7 | 0.448 |
| TNF-α | 0.1±0.0 | 0.1±0.0 | 0.265 |
| Chronic BD | | | |
| IL-1RA | 221.9±132.5 | 235.4±145.7 | 0.195 |
| IL-6 | 486.5±271.4 | 605.2±1598.5 | 0.294 |
| NSE | 7210.6±1060.7 | 9620.8±1013.1 | 0.195 |
| S100B | 517.6±545.7 | 592.9±515.4 | 0.300 |
| TNF-α | 261.4±107.9 | 250.3±57.2 | 0.335 |

BD: bipolar disorder, IL-1 RA: IL-1 receptor antagonist, NSE: neuron-specific enolase, TNF-α: tumor necrosis factor-alpha

## DISCUSSION

This is the first study to examine cytokine levels, neuronal loss levels (NSE), and gliosis levels (S100B) at different stages of BD. Although prior research suggested that inflammation was increased in patients with chronic BD, it was not known whether these defects were inherent or had emerged as an unavoidable adverse effect of neuroprogression (Modabbernia et al. 2013). Our results suggest that BD is associated with changes in neuronal survival and cytokines, which vary from early to chronic stages of illness. TNF-α, IL-1RA, and IL-6 levels were all higher in the chronic BD group, which supports neuroprogression in BD (Berketak 2011, Cetin et al. 2012, Tsai et al. 2017).

Moreover, post-hoc analysis in our study showed that there were no differences between patients with early-stage BD and healthy controls in terms of cytokine levels. This finding underlines the neuroprogression by showing elevation of cytokine levels from early to chronic stages.

A meta-analysis showed that IL-6 levels tended to show a near-significant increase in patient population, with higher levels in mania (Brietzke et al. 2009, Kapczinski et al. 2011, Modabbernia et al. 2013, Queissner et al. 2018). In our study, IL-6 levels were higher in patients with chronic BD; however, there was no significant difference in terms of mood episodes. Another meta-analysis showed no difference between patients with mania and euthymia, which supports our findings (Munkholm et al. 2013b). In adolescents, a recently published study on IL-6 levels showed no difference between patients with early-stage BD and healthy controls, consistent with our results (Scola et al. 2016).

Although the data of three studies on patients with chronic BD showed no differences in IL-1Ra levels, sub-analyses excluding depressive subgroups revealed a significant increase (Liu et al. 2004, Tsai et al. 2001). In our study, the percentage of patients with mania was higher than in the three studies described above, which may be the reason why levels of IL-1Ra were higher in the chronic BD group.

TNF-α is referred to as the most popular and promising inflammatory marker. All three large meta-analyses showed consistent data on TNF-α levels. TNF-α levels were

significantly higher in the patient groups, and patients with mania had the highest TNF-α levels (Guloksuz et al. 2012, Modabbernia et al. 2013, Munkholm et al. 2013a, Munkholm et al. 2013b). However, in our study, mood episode subgroups showed no differences with regard to TNF-α levels. This is consistent with a previous report emphasizing that TNF-α and soluble TNF-α receptors were biomarkers of BD independently of the episode type (Brietzke et al. 2008, van den Ameele et al. 2017). Significant correlation between TNF-α and MADRS scores emphasizes that neuroinflammation in depressive patients play a primary role and is consistent with previous reports (Birur et al. 2017, Pawlowski et al. 2014). Thus TNF-α levels may be used as a biomarker for the course of illness.

S100B can be regarded as a biomarker for glial alterations, neuro and glioplasticity. In a review of Schroeter et al, S100B levels were found to be higher in the chronic BD group (Schroeter et al. 2011). Especially during episodes of mania, patients have shown an increase in S100B levels, which suggests that S100B could be a putative marker of astrocytic activity (da Rosa et al. 2016, Tsai et al. 2017). Although patients had higher S100B levels than healthy controls in an early-stage BD study, the authors noted that as the expected neurodegenerative characteristics of S100B. (Machado-Vieira et al. 2002). In our study, patients with chronic BD had higher S100B levels than the early-stage BD group and the healthy controls. Moreover, IL-1Ra and IL-6 levels correlated with S100B in the chronic BD group, which appears to be particularly associated with gliosis. Our findings suggest that glial activity alterations may be a major underlying pathophysiologic mechanism of BD because IL-1RA and IL-6 are produced by glial cells (Rajkowska 2000).

In patients with early-stage BD, NSE levels were significantly lower than in controls in two studies in which a hypothesis of energy dysmetabolism was suggested (Machado-Vieira et al. 2007, Wiener et al. 2013). On the other hand, there are also studies of unipolar depression showing patients with an increase in cerebrospinal fluid NSE levels (Schmidt et al. 2015). NSE is a biomarker which predicts neuronal damage level. In our study, the increase in NSE levels supported the neuronal loss hypothesis in patients with chronic BD. In both patient groups, IL-6 levels positively correlated with NSE levels, which supports the association of neuronal death with inflammation (Murray et al. 2011). Neuronal loss may also be associated with the progressive course of BD.

Subanalyses showed that there is no relation between psychotic symptoms in bipolar disorder and neuroinflammatory markers, therefore inflammatory changes and glial activity increment are thought not to affect the limbic system which is responsible for the psychotic symptoms and that they emerge in different brain regions at same time.

As a major limitation of our study, we could not evaluate the drug effect on the markers of inflammation and neurodegeneration because the study design did not contain patients with BD who were drug-naïve due to difficulties of collecting samples in the early-stage group. The patient group was on different medication combinations which caused heterogeneity. Thus, different medication subgroups were not large enough to make a powerful analysis which required larger patient groups. Although alcohol dependency was excluded, patients and healthy controls who smoked were not classified in terms of cigarette pack days. Although drug abuse was evaluated in terms of self-report, lack of toxicology screen comprises an important limitation. Lack of obesity evaluation was another major limitation because body mass index is known to have effects on inflammation. Lack of age matched control group was another limitation. However, correlation analyses showed that there was no significant correlations between age, illness duration and neuroinflammatory markers in all groups. Therefore age and illness duration is thought not to effect inflammation parameters. Lastly, study design was cross-sectional, thus our study may not inform clearly about temporal course of the inflammatory progress.

## CONCLUSION

Several candidate biomarkers are emerging and hold promise to elucidate the underpinnings of BD, facilitate early identification, personalize treatment, and improve outcomes. Although previous research suggested that inflammation was increased in patients with chronic BD, to our knowledge, this is the first pilot study to evaluate both chronic and early stage groups in terms of inflammation, gliosis, and neuronal loss. The present findings support in part the hypothesis that inflammation starts at later stages of BD, presumably as an associated effect of gliosis and neuronal loss, which appear to be particularly associated with IL-1RA and IL-6 activity. TNF-α is associated with the progression of certain psychiatric symptoms and thus might be a useful prognostic marker in patients withBD. The present findings underline the importance of evidence that implicates a dysregulation in inflammation and neurodegeneration in the pathophysiology of BD, which warrants additional evaluation in future prospective longitudinal studies.

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