EVALUATION OF MONOCYTE SUBPOPULATIONS IN BIPOLAR DISORDER AND ITS ASSOCIATION WITH NEUROCOGNITIVE DETERIORATION

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Abstract

PURPOSE Bipolar Disorder (BD) is characterized by changes in mood and deterioration in neurocognitive functioning. Our preliminary data found significant immune activation in these patients. Changes in monocytes and their subsets have been described in several diseases but studies are scarce in BD patients related to mood episodes and neurocognitive deterioration. We aimed to investigate the association between the percentage and activation stage of different monocyte populations and mood changes with cognitive deterioration.

METHODS Thirty-seven participants (26 cases and 11 controls) were recruited as part of the inflammatory cytokines and neurocognitive functioning in bipolar disorder patients across mood episodes project. The percentage of monocyte subpopulations (CD14/CD16) and the activation stage by HLADR levels were evaluated using Flow Cytometry. Neuropsychological tests were used to measure different cognitive domains. All statistical analyses were performed with SPSS version 29 and Graph Pad Prism version 9.5.1 software for Mac. Statistical significance was considered at $p \leq 0.05$.

RESULTS BD patients had an increased number of circulating peripheral blood monocytes compared to healthy controls. Serum biomarker concentration showed a significant correlation between HLADR levels in CD14++CD16+ and cognitive deterioration in BD patients vs healthy controls (r = 0.482, p = 0.005). We also found a significant correlation between the percentage of activated CD14+CD16- HLADR+ and neurocognitive deterioration in BD (r = 0.457, p = 0 .032).

CONCLUSIONS The findings evidence a significant immune activation in BD, including a higher proportion of activated monocytes and inflammatory signals. Worse neurocognitive functioning was found in bipolar patients.

Introduction

BD is characterized by discrete episodes of changes in mood (depression and/or mania) and euthymia. Individuals with BD are vulnerable to a variety of physical conditions such as hypertension, hyperlipidemia, type 2 diabetes, and metabolic syndrome. This disease vulnerability in BD patients can be attributed to higher inflammation. Inflammatory cytokines are elevated in BD patients especially during mood episodes and euthymia. These inflammatory signals in mood episodes has been reported to be a predictor of future neurocognitive deterioration. Besides cytokines, specific monocytes are involved in diseases such as Alzheimer Disease (AD) that led patients to exhibit cognitive impairment. The aim of this study is to investigate the association between the percentage and activation stage of different monocyte subpopulations and mood changes with cognitive deterioration.

Methodology

The Institutional Review Board (IRB) of the University of Puerto Rico, Medical Sciences Campus approved this study. This pilot project was a case-control study. Thirty-seven participants (26 cases and 11 controls) were recruited. Men (27%) and women (73%) between the ages of 21 to 55 years old were included. Four sessions were carried out. We assessed the clinical features and cytokine/ chemokine plasma levels of participants. The percentage of monocyte subpopulations (CD14/CD16) and the activation stage by HLADR levels were evaluated using Flow Cytometry. All subjects were interviewed by a trained psychiatrist. Each participant was fasting before the blood sample was taken. Neuropsychological tests were used to measure verbal fluency, speed processing, working memory/attention, visuospatial skills, verbal learning, executive functions, and motor skills. Descriptive statistics were used to calculate the demographic characteristics of the sample. All statistical analyses were performed with SPSS version 29 and Graph Pad Prism version 9.5.1 software for Mac. Statistical significance was considered at $p \leq 0.05$.

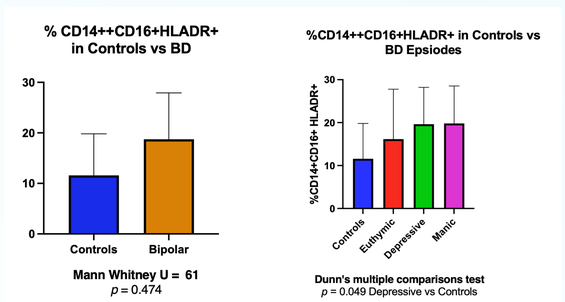
Results

Table 1.

Descriptive Statistics	N	Minimum	Maximum	Mean	SD
Age (years)	37	21	54	34.7	9.8
Education (years)	37	12	26	16.8	2.9
BMI (Kg/m²)	37	18	47	30.22	6.9

Table 2.

BD episodes	Euthymic	Depressive	Manic
%	24	52	24



Figures 1A-B. Percentage of CD14++CD16+HLADR+ in Controls vs BD (A). Percentage of CD14++CD16+HLADR+ in Controls vs BD episodes.

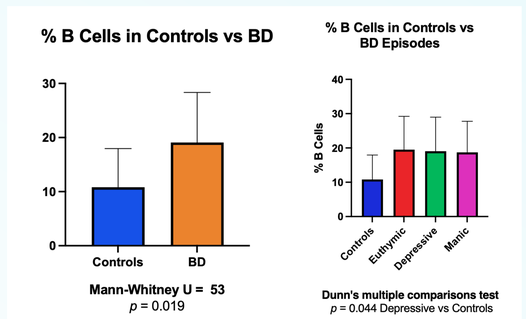


Figure 2. A-B Percentage of B Cells by groups and episodes in BD patients.

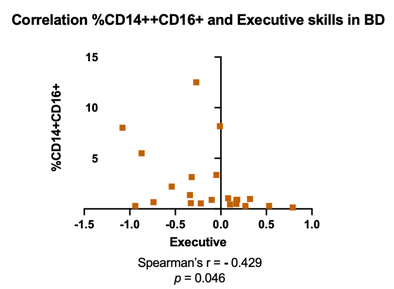


Figure 3. Significant negative correlation between Executive skills and %CD14++CD16+ in BD patients. Patients with less percentage of this monocyte have better performance in this domain.

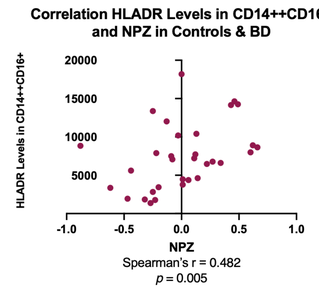


Figure 4. Significant correlation between HLADR levels in CD14++CD16+ and neurocognitive functioning of controls and BD.

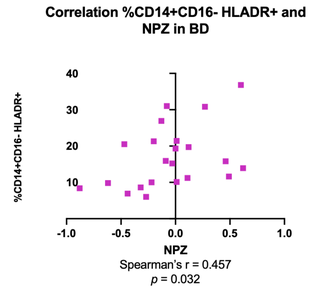


Figure 5. Significant correlation between %CD14+CD16- HLADR+ and neurocognitive functioning in BD

Results

Monocytes' subpopulations in BD. Patients had an increased number of circulating peripheral blood monocytes compared to controls. The percentage of CD14++CD16+HLADR+ in BD was more than in controls (Figure 1A), and when we include the episodes in BD, patients with depressive episodes have significantly more concentration (Figure 1B). In the case of B Cells, we found more percentage activation in BD patients vs controls (p = 0.019) (Figure 2A). We analyzed different BD episodes and found a significant difference between controls and bipolar depression (Figure 2B). B cells are essential for the adaptive immune system and antibody production but also are related to pro and anti-inflammatory cytokines responses. A significant negative correlation was found between %CD14++CD16+ intermediate monocyte and Executive skills in BD (Figure 3). BD patients with more percentage of this monocyte have the worst performance in this domain. Serum biomarker concentration significantly correlated with HLADR levels in CD14++CD16+ and cognitive deterioration in BD vs controls (r = 0.482, p = 0.005) (Figure 4). We also found a significant correlation between the percentage of activated CD14+CD16- HLADR+ and neurocognitive deterioration in BD (r = 0.457, p = 0 .032) (Figure 5).

Conclusion

The findings evidence a significant immune activation in BD, including a higher proportion of activated monocytes and inflammatory signals. Inflammatory signals are elevated in BD patients during mood episodes (depression, mania) and euthymia. These inflammatory signals are clinically important as heightened inflammatory burden is also known to result in worse neurocognitive impairment. BD patients presented a unique immunological profile compared to controls in our sample.

Limitations. Small sample size, crossectional study, and all patients were using mood-stabilizing medications that could influence immune functions.

Future directions. Our next steps will be the development of an R01 proposal, a longitudinal study with adequate sample size.

Acknowledgment

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