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Dysfunctional response of monocytes/macrophages in late-stage bipolar disorder

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Introduction: There is a growing body of evidence suggesting the involvement of an immune response dysfunction in the pathogenesis of bipolar disorder (BD). Knowing that peripheral cytokines levels are abnormal in patients with BD, we evaluated the pattern of macrophages polarization, classic (M1) or alternative (M2), and how this pattern changes from early to late stages of BD.

Methods: Patients with bipolar disorder (n=20) according to DSM-5 and in remission period were recruited from Bipolar Disorders Program. They were classified into early and late stages based on functional status criteria. The control group (n=10) consisted of healthy volunteers. Mononuclear cells were collected from the interphase of peripheral blood obtained from all participants. These cells were isolated and then differentiated with macrophage colony-stimulating factor. Posteriorly, monocyte-derived macrophages (M0) were exposed to IFN-γ plus LPS or to IL-4 for 24 hours to induce their polarization into the M1 or M2 phenotype, respectively. After 24 hours, supernatants were collected and cytokines (IL-1β, IL-6, IL-10 and TNF-α) were measured by multiplex assay (HSTCMAG-28SK). Phagocytosis assay was used to analyze the functionality of M0, M1 and M2 by means of fluorescence and quantification was done on Accuri C6 Flow Cytometer. Statistical analyses were performed using SPSS software and GraphPad Prism. Demographic data were compared using t Student, One-way ANOVA or Chi-square tests as appropriated. Cytokine secretion were analyzed using Kruskal-Wallis' followed by Mann-Whitney's tests and p values < 0.05 were considered significant.

Results: No demographic differences were found among the three groups. As expected subjects with late stage of BD had poor functioning (40.78±14.66) compared to early stage (11.33±10.06) and healthy volunteers (5.10±6.24; F=29.181; p=0.001). The Kruskal-Wallis test revealed significant differences between three groups in the secretion of cytokines. In particular, IL-1β secretion by M1 (U=9; p=0.004) as IL-6 secretion by M0 (U=12; p=0.012), M1 (U=12; p=0.021) and M2 (U=16; p=0.031) and IL-10 by M0 (U=11; p=0.009) and M1 (U=15; p=0.046) from late stage BD patients were reduced in relation to early stage. Late stage BD patients had decreased IL-1β secretion by M0 (U=16; p=0.009) and M1 (U=9; p=0.004), IL-6 by M1 (U=10; p=0.003) and M2 (U=16; p=0.031), IL-10 by M1 (U=13; p=0.014), and TNF-α by M0 (U=11; p=0.006), M1 (U=10; p=0.004) and M2 (U=17; p=0.022) compared to healthy controls. In general, no significant differences were found between early stage BD and control group in cytokines secretion. In phagocytosis assay, we observed a tendency to a lower phagocytosis index in late stage BD patients when compared to early stage in the three induced phenotypes M0, M1 and M2 (p= 0.06).

Conclusion: Our findings support a causal dysfunctional response of macrophages for conversion, modulation and function of M1 and M2 phenotypes from M0, which was most evident in the late stages of BD. Also, macrophage function was defective in late BD patients. We hypothesize that persistent microenvironmental and systemic changes that occur during the progression of the disease, might promote exhaustion of the immune system. In this regard, it is plausible to speculate that this failure of the immune system to regulate and counterbalance a peripheral inflammatory response may contribute to structural and neurocognitive changes commonly observed in the advanced stages of the illness.