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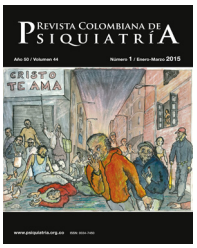

Review article

Inflammatory Markers in the Staging of Bipolar Disorder: A Systematic Review of the Literature

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ABSTRACT

Background: Previous studies suggest that inflammatory molecules play an important role in the pathophysiology of Bipolar Disorder (BD). The evidence suggests that BD may present a progressive course. Therefore there are theories that postulate the relationship between progression and stages of the disease with distinct peripheral biomarkers.

Objective: The aim of this study was to carry out a systematic review of the literature of studies about the association between peripheral inflammatory markers and clinical variables related with staging in BD patients.

Methods: We conducted a systematic review using electronic databases: PubMed, SciELO, LiLACS and PsycINFO. Keywords were divided into inflammatory markers and, BD and staging. Studies involving euthymic BD patients, studies evaluating peripheral biomarkers and studies correlating these with clinical variables related to neuroprogression or stage of BD were included.

Results: We present and discuss the methods and findings of ten articles. The inflammatory markers were measured with different techniques and show some contradictories results. The TNF superfamily and inflammatory cytokines may have a relationship with the neuroprogression of the disease.

Conclusions: This study suggests that TNF and ILs could play a role in neuroprogression. However, longitudinal studies are needed to clarify the relationship between factors associated with neuroprogression.

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Marcadores inflamatorios en la estadificación del trastorno bipolar: una revisión sistemática de la literatura

Palabras clave:
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RESUMEN

Introducción: Estudios previos indican que las moléculas inflamatorias tienen un papel importante en la fisiopatología del trastorno bipolar (TB). La evidencia apunta a que el TB puede presentar un curso progresivo. Por lo tanto, existen teorías que han postulado una relación entre la progresión y los estadios de la enfermedad con diferentes biomarcadores periféricos.

Objetivo: El objetivo de este estudio es realizar una revisión sistemática de la literatura de los estudios sobre la asociación entre los marcadores inflamatorios periféricos y las variables clínicas relacionadas con la estadificación en los pacientes con TB.

Métodos: Se llevo a cabo una revisión sistemática usando las bases de datos electrónicas PubMed, SciELO, LiLACS y PsycINFO. Las palabras clave se dividieron en marcadores inflamatorios y TB y estadificación. Se incluyeron estudios que evaluaron a pacientes con TB en fase de eutimia, estudios que evaluaron biomarcadores periféricos y estudios que correlacionaron dichos marcadores con las variables clínicas relacionadas con la neuroprogresión o estadificación del TB.

Resultados: Se presentan y se discuten los métodos y los hallazgos de 10 artículos. Los marcadores inflamatorios se determinaron con diferentes técnicas y mostraron resultados contradictorios. La superfamilia del factor de necrosis tumoral y las citocinas inflamatorias podrían tener una relación con la neuroprogresión de la enfermedad.

Conclusiones: El presente estudio indica que el factor de necrosis tumoral y las intereucinas pueden tener un papel en la neuroprogresión del TB. Sin embargo, se requieren estudios longitudinales con el fin de clarificar la relación entre los factores asociados con la neuroprogresión.

Introduction

Bipolar disorder (BD) is a chronic, recurring and potentially progressive disease that affects between 1% and 3% of the population, and is one of the conditions that causes the most loss of life due to disability.[1,2] It was previously thought that its clinical characteristics and nature were only associated with affective episodes, however in recent years cognitive impairment has been described, primarily in memory, attention span and executive function, including during the euthymia,[3] as well as long-term progressive clinical deterioration in some patient subgroups.[4] Of the neurobiological explanations it has been proposed that the disease exhibits neuroprogression, which would indicate a worse outlook, a rise in relapses and possible neuroanatomical, functional and biochemical changes.[5,6] The allostatic load theory has been proposed to explain the neuroprogression and division in stages of the disease.[7,8] In this theory a physiological wear and tear in a non adaptive way in response to multiple stressors in bipolar patients could be associated with oxidative stress, inflammation and neurotrophin expression.[9,10] Also, various candidate biomarkers have been described for the stages of the disease, and there is consensus to search neuroimaging, peripheral inflammatory markers and genetic markers.[11]

Neuroprogression has led to the formulation of clinical staging models for BD I,[12–16] which could be useful for diagnosis and specific interventions for each stage.[14] The importance of staging classification systems lies in the possibility of a stage specific treatment regimen that could prevent the progression to late stages or remission to early stages.[17,18] The International Society for Bipolar Disorders proposes dividing the staging into early and late, as well as the need for studies that validate and confirm the use of these models.[14] The division of the proposed staging models is based on clinical variables such as the number of episodes, the length of illness, psychosocial functioning, neurocognition, quality of life and response to the treatment.[14,18,19] But, it is essential include biological markers of progression that improved the physiopathological understanding of the disease, strengthen the clinical staging models and the search for other therapeutic targets.[9,14] Studies which evaluated inflammatory markers have described the key role played by interleukins (IL), tumor necrosis factor (TNF) and other inflammatory factors in the physiopathology of BD.[20] Many studies have evaluate the association between inflammatory biomarkers and BD.[21,22] However, studies that sought the association of inflammatory biomarkers with staging are scarce.[14]

The goal of this study was to carry out a systematic review of the literature for all available studies that evaluated the serum or plasma levels for inflammatory markers in patients with BD, and its association with stages or clinical variables related to the staging of the disease.