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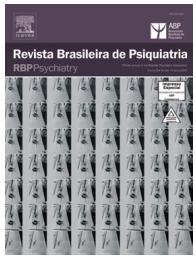

SPECIAL ARTICLE

Staging and neuroprogression in bipolar disorder: a systematic review of the literature

Clarissa Severino Gama,[1,2] Maurício Kunz,[1,2] Pedro V.S. Magalhães,[1,2] Flavio Kapczinski[1,2]

[1]Laboratory of Molecular Psychiatry, Universidade Federal do Rio Grande do Sul, Brazil
[2]Medical Graduate Program: Psychiatry, Universidade Federal do Rio Grande do Sul, Brazil

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DESCRIPTORS:
Bipolar Disorder;
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Abstract
Introduction: The use of clinical staging models is emerging as a novel and useful paradigm for diagnosing severe mental disorders. The term "neuroprogression" has been used to define the pathological reorganization of the central nervous system along the course of severe mental disorders. In bipolar disorder (BD), neural substrate reactivity is changed by repeated mood episodes, promoting a brain rewiring that leads to an increased vulnerability to life stress. *Method:* A search in the PubMed database was performed with the following terms: "staging", "neuroprogression", "serum", "plasma", "blood", "neuroimaging", "PET scan", "fMRI", "neurotrophins", "inflammatory markers" and "oxidative stress markers", which were individually crossed with "cognition", "functionality", "response to treatments" and "bipolar disorder". The inclusion criteria comprised original papers in the English language. Abstracts from scientific meetings were not included. *Results:* We divided the results according to the available evidence of serum biomarkers as potential mediators of neuroprogression, with brain imaging, cognition, functioning and response to treatments considered as consequences. *Conclusion:* The challenge in BD treatment is translating the knowledge of neuronal plasticity and neurobiology into clinical practice. Neuroprogression and staging can have important clinical implications, given that early and late stages of the disorder appear to present different biological features and therefore may require different treatment strategies.

Corresponding author: Clarissa Severino Gama. Hospital de Clínicas de Porto Alegre/CPE, Molecular Psychiatry Laboratory, Rua Ramiro Barcelos, 2350, Prédio Anexo, 90035-903 Porto Alegre, RS, Brazil.
Phone: +55 51 33598845; fax: +55 51 33598846. E-mail: clarissasgama@gmail.com

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Introduction

The use of clinical staging models is emerging as a novel and useful paradigm for diagnosing severe mental disorders.[1] The staging concept is particularly practical, as it can differentiate early, milder clinical phenomena from those that accompany illness progression and chronicity.[2] The logic of staging is based on accessing the clinical features of a patient within a longitudinal perspective of illness development to provide different treatment approaches according to their specific pathophysiological, symptomatic and structural changes at each stage of illness.[3]

The term "neuroprogression" has been increasingly used to define the pathological reorganization of the central nervous system (CNS) along the course of severe mental disorders.[4] This reorganization could arise as the result of several insults, such as inflammation and oxidative stress.[5] In bipolar disorder (BD), neural substrate reactivity is changed by repeated mood episodes, ultimately promoting a brain rewiring that leads to an increased vulnerability to life stress.[6-8]

Recurrent episodes influence the outcome of BD by increasing a patient's vulnerability to subsequent episodes and reducing the treatment response.[9] An episode-dependent deterioration pattern has been widely described in serum biomarkers,[4,10] brain imaging[11,12] and functioning.[13-16] Therefore, staging models emphasizing the assessment of patients in the interepisodic period[17-20] have been proposed to personalize and optimize treatments for BD.[21]

The neurobiological mechanisms of more pronounced neuroanatomical brain changes in patients with multiple mood episodes of BD appear to include increased oxidative stress, increased pro-inflammatory markers and a deficit in neuroprotection.[4] Although definitive empirical evidence is lacking, staging and neuroprogression can be conceived of as two facets of the same phenomenon (Figure 1).[22]

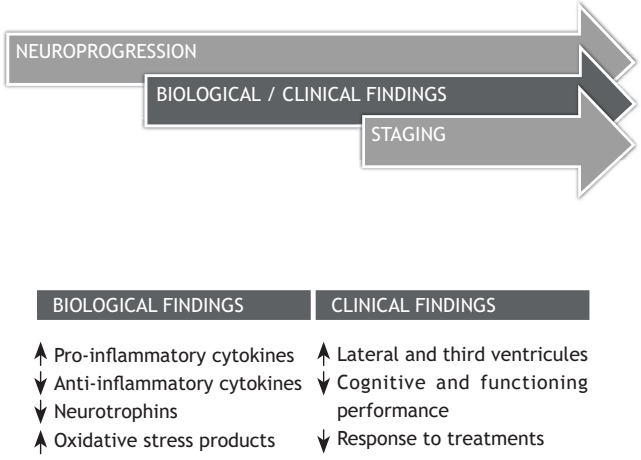

Figure 1 Linking neurobiological and clinical findings to neuroprogression and staging.

Methods

A search in the PubMed database was performed with the following terms: "staging", "neuroprogression", "serum", "plasma", "blood", "neuroimaging", "PET scan", "fMRI", "neurotrophins", "inflammatory markers" and "oxidative stress markers", which were individually crossed with "cognition", "functionality", "response to treatments" and "bipolar disorder" (BD).

The inclusion criteria comprised original papers in the English language. Abstracts from scientific meetings were not included. There was no limit for the year of publication, and the search included papers until July 2012.

The search retrieved 70 articles, from which 65 were included. The remaining 5 articles were excluded for the following reasons: case report (n = 2), comment on an original paper (n = 1) and studies focusing on other disorders and conditions (n = 2).

Results

We divided the results according to available evidence of serum biomarkers as potential mediators of neuroprogression, with brain imaging, cognition, functioning and response to treatments considered as consequences.

Serum biomarkers

Data from different lines of research converged to the brain-derived neurotrophic factor (BDNF) as an important contributor to neuroplastic changes in BD. Serum BDNF levels have been shown to be decreased during depressive and manic episodes and to return to normal levels in euthymia.[23-26] In this line, a decrease in BDNF levels acts as a state-dependent biomarker for mood episodes in BD.[27,28] It has also been shown that decreased BDNF levels are found in chronic or late-stage individuals with BD, in comparison to patients in early stages of the illness,[29] and an overall accelerated age-related decrease of BDNF was discovered in patients with BD.[30] In young adults with bipolar disorder recruited from the general population, BDNF levels tend to be similar to those of healthy controls.[22]

Factors that negatively influence the course of BD, such as life stress and trauma, have been shown to be associated with a decrease in serum BDNF levels among people with bipolar disorder.[31] However, effective treatments, such as lithium and divalproex, have proven to prevent cellular atrophy, to have anti-apoptotic properties and to increase BDNF levels.[32]

Available evidence indicates that BD and inflammation are linked through shared genetic polymorphisms and gene expression, as well as altered cytokine levels[33] during acute episodes[34,35] and euthymia.[36,37] It has been suggested that inflammatory cytokines, particularly TNF-α, may play a critical role in the process of changes in neuroplasticity, cell resilience and neuronal survival.[38,39] Additionally, BDNF and TNF-α serum levels combined have been proposed as staging biomarkers for BD.[17] When early- and late-stage patients with BD were compared, IL-6 and TNF-α were elevated in both groups, while IL-10 levels were higher in the early stages. However, TNF-α was higher in late stages than in early.

BD is associated with an imbalance in oxidative biology and often involves an increase in lipid damage that is measured by thiobarbituric reactive substances (TBARS) and