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EDITORIAL

Biological mechanisms underlying neuroprogression in bipolar disorder

Bipolar disorder (BD) is a psychiatric illness typically characterized by recurrent episodes of mania and depression associated with a high rate of medical and psychiatric comorbidities. Currently approved treatments for BD include lithium, valproate, and antipsychotics. However, many bipolar patients do not respond adequately to these medications and continue to have recurrent mood episodes, residual symptoms, functional impairment, psychosocial disability, and significant medical and psychiatric comorbidity. Several studies have reported the reduction in neuronal and glial density, mainly in limbic regions, in patients with BD.

It has been postulated that this disorder might be associated with temporal progression in phenomenology, treatment response, neurobiology, and functional impairment. Therefore, different stages of BD are associated with distinct neurobiological mechanisms, such as mitochondrial dysfunction, oxidative stress, inflammation and neurotrophic dysfunction. These biological markers may be altered in distinct stages of BD (early or late). In addition to the biochemical alteration, BD is associated with neuroanatomical changes at the onset of this disorder, which are exacerbated by the occurrence of further episodes. Accordingly, the present issue of the Revista Brasileira de Psiquiatria will address mechanisms of neuroprogression in BD.

Oxidative stress and energetic metabolism appear to be closely linked in BD. The mitochondrial dysfunction in BD is associated with mitochondrial DNA deletion/mutation/polymorphism in the neural tissue of BD patients.[1] These alterations can be accompanied by changes in the complex of the mitochondrial electron transport chain, which can lead to an elevated level of reactive oxidative species and an imbalance between oxidant and antioxidant mechanisms. In contrast, oxidative stress may inhibit mitochondrial electron transport chain complexes, leading to a decrease in ATP production and cellular dysfunction. Antioxidant enzyme changes and oxidative damage to lipid and proteins have been widely reported in BD patients, and this may be the explanation for the apoptosis-mediated cellular death and, consequently, decrease in brain volume observed in BD.[3] The excessive increase in reactive oxygen species, resulting in oxidative stress and subsequent oxidative damage to lipids, proteins and nucleic acids, can lead to the activation of a signaling pathway of cell death. In fact, protein and mRNA levels of BAX and GSK-3β, molecules known as apoptotic factors, were found to be altered in BD.[2,3] Moreover, studies on BD brains have demonstrated decreased levels of Bcl-2 and brain-derived neurotrophin factor (BDNF), which are anti-apoptotic factors.[4]

Interestingly, there is evidence showing that oxidative stress may be increased under conditions in which BDNF is decreased in BD.[5] Studies show that mood stabilizers, such as lithium and valproate, increase BDNF levels and protect against oxidative damage. BDNF is a neurotrophin that is essential for neuronal survival, synaptic plasticity, and cortical development. Thus, the impairment in BDNF levels observed in BD patients may contribute to brain atrophy and progressive cognitive changes observed in this disorder. In addition, reduced levels of peripheral BDNF are found during mania and depression but not in euthymic episodes of BD patients, further emphasizing the role of this neurotrophin in neuroprogression of the illness.

It is important to emphasize that oxidative stress is an important activator of microglia, which generate pro-inflammatory cytokines; in turn, oxidative stress might mediate inflammatory process. In fact, it has been postulated that inflammation is involved in BD because elevated levels of cytokines are associated with both depression and mania. These cytokines include interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNFα). It is believed that cytokine levels are altered during mania and depression phases as well as in the asymptomatic period of the disorder. This link between BD and inflammation can occur due to the sharing

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of genetic polymorphisms and gene expression. Moreover, it has been suggested that inflammation might be associated with cognitive deficits observed in BD patients.[1]

All the mechanisms mentioned above suggest that toxicity accumulates during the course of the illness, which might explain the increasing clinical severity with BD progression (increasing number of episodes). One caveat to consider is that further studies are needed to clarify the neuroprogression mechanism in BD patients. A better understanding of this process is important to identify biological markers that could become potential treatment targets in different stages of the disorder. Therefore, this issue of the Revista Brasileira de Psiquiatria will contribute to enhance knowledge and advance research efforts for an effective therapy for early stage BD, reducing the disability associated with disease progression. These studies open the door to the development of rational strategic interventions for different stages of BD.

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