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FOOD FOR THOUGHT

Would be IL-6 a missing link between chronic inflammatory rheumatism and depression after chikungunya infection?

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Dear Sir,

As has been previously reported [1], chikungunya virus disease (CHIK) has emerged in Latin America as a significant acute infectious disease condition, but also with multiple implications during its chronic phase, including the post-chikungunya chronic inflammatory rheumatism (pCHIK-CIR), now well-documented, particularly in Colombia, where around 50% of patients go with clinical rheumatological, but even systemic disease, beyond 12 weeks after infection (chronic phase) [2, 3]. Among the systemic reported conditions, depression has been described in some studies [4].

Major depressive disorder is a severe mental illness. It causes disability and even mortality worldwide [5, 6]. Depression is a remarkable problem, with relevant direct and indirect costs, being considered a major public health issue [5]. The pathogenesis of this disorder is still unknown, but there are some evidences that range from several factors or theories: cognitive, hypothalamic–pituitary–adrenal axis dysfunction, neurodegenerative disorders, stress generation, social, psychological and environmental issues, as well inflammation, among others [5].

Among the last of them, depressive symptoms have been linked to an immune response [5–7]. This consideration is based on the highly interrelated extensive relationships between the immune, endocrine and central nervous (CNS) systems.

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During periods of increased stress or chronic illness, pro-inflammatory cytokines are released. Chronic exposure to cortisol and cytokines reduces the availability of monoamines, such as serotonin, dopamine and norepinephrine, by influencing synthesis and reuptake. These monoamines play an important role in emotion regulation [5].

The hippocampal and prefrontal cortex are widely associated with the occurrence of mood disorders. The hippocampus is sensitive to cortisol toxicity and elevated pro-inflammatory cytokines; reduction of hippocampal volume has a negative effect on affective modulation also [5]. Neuroinflammation activation leads also to abnormal function in the prefrontal cortex [6].

Among the involved cytokines, interleukin-6 (IL-6) plays an important role in the immune response and acute phase reactions. It is a multifunctional cytokine that regulates the growth and differentiation of various tissues [6]. This cytokine is a versatile protein primarily categorized as proinflammatory but also anti-inflammatory one. It can be released from several tissues including white blood, endothelial and epithelial cells, astrocytes, adipose tissue, microglia and neurons. IL-6 contributes to stress sensitivity in the CNS. IL-6 is considered a relevant biomarker for depression, and it has a potential therapeutic target for mood-related disorders [7].

During acute and chronic chikungunya infection, cytokines, such as IL-6, have been shown to play important roles, as has been also reported in other arthritides, including epidemic polyarthritis caused by Ross River virus and rheumatoid arthritis [8]. At the chronic phase, levels of IL-6 were found to be associated with persistent arthralgia providing a possible explanation for the etiology of arthralgia that affects numerous CHIKV-infected patients [9]. Even more, recently, high scores at the disease activity index 28 (DAS-28) and World

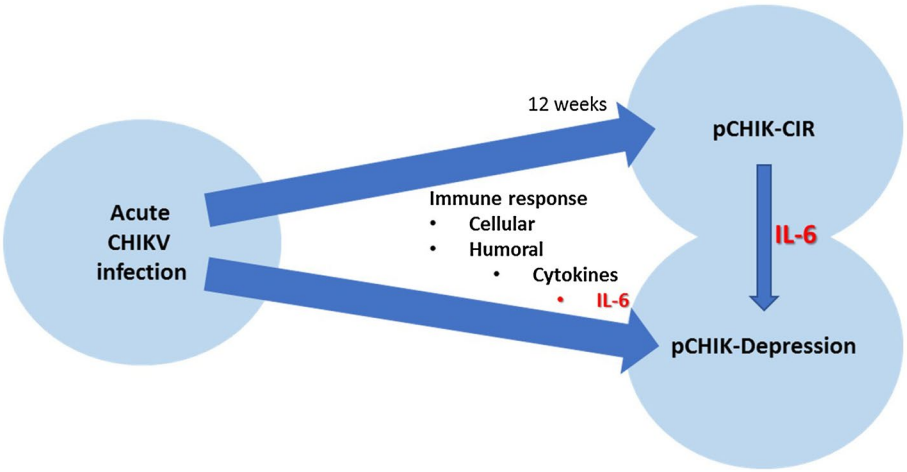

Fig. 1 Proposed model of relationships between acute and chronic infection and depression mediated by IL-6 in chikungunya

Health Organization Disablement Assessment Schedule II (WHODAS-II) questionnaires (used to evaluate the clinical evolution of patients with CHIKV infection) and high serum levels of IL-6 in those with acute infection may be predictors for developing subacute and chronic disease [10]. Then, seems clear that the question, would be if IL-6 is a missing link between chronic inflammatory rheumatism and depression after chikungunya infection? Solving the puzzle, during acute CHIKV infection, levels of IL-6 and other cytokines increase (Fig. 1); this would be one of the biological factors related to stress sensitivity together with other social factors that would lead to post-CHIKV depression. Also, after the 12-week period, moving to the chronic phase, in those presenting clinical disease of pCHIK-CIR, IL-6 is also increased (Fig. 1), and this would be also during chronic phase a risk for depression after the acute stage of CHIKV infection.

Given these considerations, IL-6 would be used in the clinical setting to predict pCHIK-CIR, as suggested in previous reports [10], but its assessment in those patients with post-CHIKV depression is also necessary. This would provide plausible mechanisms in the complex area of cytokine signaling that could explain the pathogenesis of CHIK chronic consequences [9], as well in the development of interventions targeting the IL-6 signaling blockade [8] in order to potentially impact on depression and pCHIK-CIR.

In recent years, the relationship between inflammatory biomarkers and CNS disorders, including depression, has been extensively studied; nevertheless, our hypothesis deserves further study [11]. Also, other inflammatory cytokines, including TNF-α, IFN-γ, IL-8 and IL-1β, coexist in a variety of clinical disorders. But, associations, such as proposed by us, remain to be elucidated. Further studies are needed to establish causality between inflammation in pCHIK-CIR and depressive symptoms.

Compliance with ethical standards

Conflict of interest No conflict of interest to declare.

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