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Letter

## Potential relationships between chikungunya and depression: Solving the puzzle with key cytokines

*Dear Editor*

We have read with interest the article of Tucker et al. [1], about the possible link of interleukin-6 (IL-6) and interleukin-2 (IL-2) with psychiatric disorders, such as depression and anxiety. As part of ongoing investigations, we have carefully reviewed the cytokine profile and evidence related to mood disorders and cytokines in the context of chikungunya (CHIK) infection, giving the fact that there are a growing number of reports of describing such mental disorders during this arbovirosis [2].

During acute and chronic chikungunya infection multiple pro-inflammatory cytokines are produced by infiltrating myeloid cells. Tumor necrosis factor-alpha (TNF-α), interferon-alpha (IFN-α), IL-6, IFN-γ [3] and monocyte chemoattractant protein-1 (MCP-1), among others, have been reported as associated cytokines and chemokines secreted by macrophages during CHIK infection [4]. In a parallel way, there are multiple cytokines linked

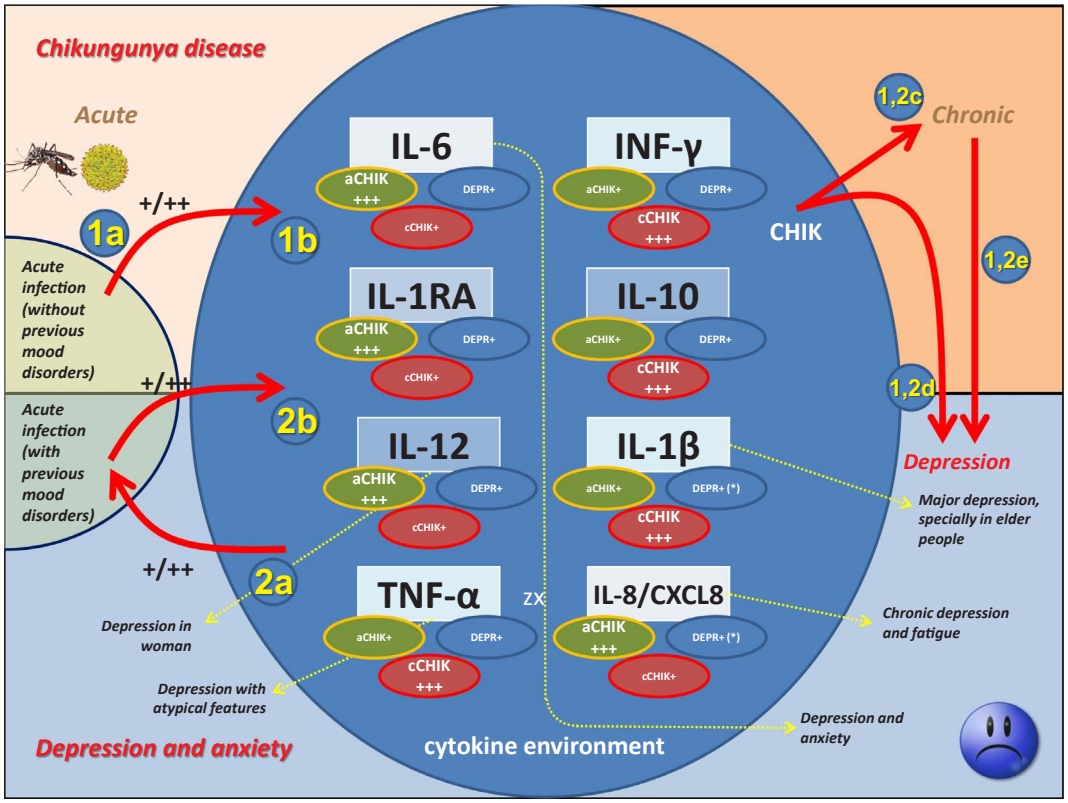


**Fig. 1.** Proposed model of relationships between CHIK infection and depression in the context of cytokines environment. **1a** In patients with acute CHIK infection (without previous mood disorders), there is an increase of multiple cytokines. **1b** Among the cytokines, shared between CHIK and depression, IL-6, IL-1RA, IL-12 and IL-8/CXCL8, are with higher levels during acute infection (aCHIK + + +), then decreasing during chronic phase (cCHIK +), whilst TNF-α, IFN-γ, IL-10, IL-1β, are in a opposite regard CHIK, during acute are increased (aCHIK +) and then with higher levels in chronic phase (cCHIK + + +). All of them are significantly found in patients with depression, with the exception of IL-1β and IL-8/CXCL8, which show controversial evidence. **1c** In patients with acute CHIK that presents increased levels of cytokines, this would progress to chronic phase. **1d** Also, such increase in cytokines would be related to the development of depression in patients with acute and chronic CHIK. **1e.** In patients with chronic CHIK, those cytokines would be also related to the development of depression. **2a**. Probably patients with previous with mood disorders, and then a dysregulated cytokine environment, would enhance the cytokines production during acute CHIK. **2b.** With already increased cytokines this would a risk factor for this dysregulated environment during CHIK infection. **2c.** As **1c**. **2d.** As **1d**. **2e.** As **1e**. Yellow dashed arrows indicate the specific associations between cytokines and clinical forms of depression. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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with depression, highlighting the IL-6, TNF-α, IL-10, the soluble IL-2 receptor, C−C chemokine ligand 2, IL-13, IL-18, IL-12, the IL-1 receptor antagonist, and the soluble TNF receptor 2 [5].

Looking the cytokines as a bridge between both conditions (CHIK and depression), we have found that at least 8 cytokines are simultaneously related to them (Fig. 1). IL-6 [6], IL-1RA, IL-12, TNF-α, IFN-γ, IL-10, IL-1β [7] and IL-8/CXCL8 are increased during acute and chronic CHIK as well in depression [1,4,5]. As has been described those cytokines are specifically related to certain varieties of depression (atypical features, in elderly people, with physical symptoms, predominantly in women, chronic depression, among others) (Fig. 1) [8]. As seen here, we have taken the pieces provided in CHIK and also in depression, and solved the puzzle with these key cytokines.

In order to proof these relationships, basic and clinical studies are necessary. These should compare levels of such cytokines between those with CHIK and depression and in those without them, adjusting by confounding factors as well by subtypes and subpopulations; which is part of our group ongoing studies.

Finally, these evidences would be of interest in potential simultaneous approaches with immunomodulator drugs for such cytokines, in the context of multifactorial and holistic assessments, during those clinical conditions in order to reduce and mitigate the impact of CHIK and depressive disorders.

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## Conflict of Interest

None of the authors report conflict of interests.

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