Relation between COVID-19 and Guillain-Barre syndrome in adults. Systematic review

Relación entre COVID-10 y sindrome Guillain-Barre en adultos. Revisión sistemática

Dear Editor:

We read with interest the recent systematic review entitled ''Relation between COVID-19 and Guillain-Barré syndrome in adults. Systematic review'' by Trujillo-Gittermann et al.[1] However, although the authors reported that they conducted the review following recommendations of PRISMA guidelines,[2] there are some important departures, which have likely introduced biases and inconsistencies we would like to draw attention.

Our first concern is the questionable way to developed the Systematic Review (SR), the authors mention in the objective: ''to analyze the evidence on the associations between COVID-19 and Guillan-Barré Syndrome (GBS)'' and in your selection studies only included case reports, design with a lower level of evidence and that does not allow to establish associations between outcomes measures.[3] Furthermore, they do not register the protocol in PROSPERO and do not take as reference the Cochrane Handbook to avoid selective reporting bias.[4,5]

Secondly, the authors not reported the risk of bias or methodological quality of studies included, introducing another bias in the quality of the SR, since it is suggested, evaluating and reporting these aspects in a complete way to see the quality of the studies in a SR.[4,6]

Regarding to the search strategy, draws attention to the flow chart diagram shown, is too general, the number of studies found by each database and the reasons for excluding studies are not reported, which makes a confusing interpretation. Furthermore, it does not report a sensitive search strategy that is required in a SR, not does it report how the [MesH] terms or ''*free text terms*'' were combined in all the databases.[7] Elements required by the PRISMA guidelines and Cochrane Handbook to prevent publication bias.[2,4,8,9]

On close inspection of the raw data used, it can be seen that there is only a descriptive analysis of the studies, which does not allow to demonstrate categorical conclusions such as ''*We found a strong association between both conditions*...'' like in the SR.[1] Moreover, if you want to show an association in a SR, you most select observational studies with effect estimators for these designs and should be performed a meta-regression analysis.[10,11]

Due to this, error may be observed in the selection, results and reports. Therefore, the results in this SR can influence the conclusion and findings of the study, Finally, the decisions or associations on its use need to be based upon unbiased summaries of the available evidence, therefore, your results should be interpreted with caution

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Conflict of interest

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Substance P, proinflammatory cytokines, transient receptor potential vanilloid subtype 1 and COVID-19: a working hypothesis☆

Sustancia P, citocinas proinflamatorias, receptor de potencial transitorio vaniloide tipo 1 y COVID-19: una hipótesis de trabajo

Dear Editor:

The main clinical feature of COVID-19 is respiratory disease of varying severity, ranging from mild upper respiratory tract involvement to severe interstitial pneumonia and acute respiratory distress syndrome, exacerbated by thrombosis of the pulmonary microcirculation.[1] However, it is increasingly apparent that the disease is multisystemic, with the virus entering the central nervous system (CNS) by retrograde neuronal transport via the olfactory nerve and/or enteric nervous system. It has also been suggested that infected leukocytes may cross the blood-brain barrier, transporting the virus to the brain; this would alter the function of brain microvascular endothelial cells, which are known to express angiotensin-converting enzyme 2 (ACE2).[2,3] Neurological signs and symptoms of SARS-CoV-2 infection, associated with expression of the ACE2 receptor in the brain, are thought to be caused by a proinflammatory response in the CNS, promoting microglial activation, the proinflammatory ''cytokine storm,'' a reduction in levels of CD4 and regulatory T cells, and ultimately the propagation of neuroinflammation.[4,5] However, the precise mechanisms explaining the direct effects of SARS-CoV-2 and the subsequent immune response on the CNS are yet to be fully understood.[6]

The neuroimmune pathway functions bidirectionally, with afferent neurons responding to peripheral immune signals and efferent neurons promoting interaction between the brain and peripheral structures.[7] Transient receptor potential vanilloid subtype 1 (TRPV1) is a nonselective ligand-gated cation channel expressed in neurons, immune cells, and type C sensory nerve fibres of the airway (upper and lower respiratory tract and lung parenchyma), among other cells; it is highly permeable to Ca^{2+} and is reported to be present at increased levels in patients with chronic cough. Mucus hypersecretion and inflammation are also associated with TRPV1 sensitisation.[8,9]

Interaction between the immune, endocrine, and nervous systems involves the participation of neuropeptides, small amino acid molecules that are able to influence immune responses and pain sensitivity through modulation of glial cell activity.[10] The pathophysiological events affecting the severity of COVID-19 have been shown to involve elevated neuronal expression of TRPV1, promoting an increase in the levels of such proinflammatory molecules as substance P and interleukin 6 (IL-6).[11]

Substance P and its selective receptor neurokinin 1 are abundantly expressed in the sensory fibres innervating the respiratory tract and lymphoid organs; such glial cells as microglia and astrocytes, and immune system cells including T cells, monocytes/macrophages, dendritic cells, and eosinophils. The neuropeptide acts as a neurotransmitter, mediating communication between the nervous and immune systems and exacerbating inflammation in such peripheral sites as the lungs.[12] Together, these mechanisms alter the immune functioning of microglia and astrocytes, which are activated in CNS inflammatory processes.[13,14]

Stimulation of TRPV1 by such respiratory pathogens as respiratory syncytial virus promotes the release of numerous molecules including substance P and IL-6.[9,11] Elevated levels of these molecules have been detected in patients with COVID-19, and seem to be associated with more severe disease.[11] All this evidence suggests the activation of a positive feedback mechanism in which increased levels of a harmful stimulus activates TRPV1, leading to greater release of substance P and proinflammatory cytokines, which would result in disease exacerbation in patients infected with SARS-CoV-2.

Despite the massive expansion of our understanding of COVID-19, no study has clarified the association between the neuroimmune function of inflammatory cytokines, neuropeptides, and the role of TRPV1 in the disease. Therefore, we may ask ourselves whether the cytokine storm is directly related with the increase in substance P levels in inflammatory processes in patients with SARS-CoV-2.

We should underscore that the secretion of substance P and cytokines involved in the cytokine storm involves the participation of TRPV1 ion channels, which can be activated by such external insults as viral infection. Therefore, it is reasonable to suppose that neuroimmune communication is established in order to protect the individual; ironically, this

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