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LETTER TO THE EDITOR

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Association between molecular markers of COVID-19 and Alzheimer's disease

To the Editor,

The COVID-19 pandemic has represented an exceptional health challenge as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has acute and chronic consequences. Acute events are mainly related to the respiratory tract; however, SARS-CoV-2 may affect the cardiovascular system, kidneys, gut, and brain. Several studies have suggested patients with more severe systemic presentations are most affected by neurological symptoms,[1,2] while data from brains of postmortem patients show that SARS-CoV-2 has neuroinvasive properties. The outcomes in the central nervous system (CNS) may be also associated with an exacerbated inflammatory process, or cytokine storm, a well-characterized effect of COVID-19 that results from an overreaction of the immune system, particularly involving the augment of interleukin 6 (IL-6). In line with this, SARS-CoV-2 may activate glial cells, thus potentially triggering chronic neuroinflammation and neurodegeneration.[3] Of note, the inflammatory response may lead to the neuronal death observed in postmortem samples of patients with COVID-19,[4] as well as SARS-CoV-2 neuroinvasion may trigger neuropathological changes.[5]

Alzheimer's disease (AD) is the most common age-related neurodegenerative disease. The main histopathological hallmarks of AD are extracellular senile plaques of amyloid-β peptides (Aβ), the product of β/γ-secretase proteolytic cleavage of the amyloid precursor protein (APP), and intracellular neurofibrillary tangles composed of abnormal hyperphosphorylated tau protein.[6] In addition, metabolic disorders and neuroinflammation have emerged as potential risk factors for dementia and AD.[6] Although inflammatory cytokine levels were shown to be relevant in the induction of metabolic disorders, chronic metabolic changes were able to induce inflammation, with a notable role of glial cells.[6] In agreement with the relevant role of inflammation in the progression of AD, increased levels of IL-6 in plasma, cerebrospinal fluid, and brain of AD patients have been reported. Mitochondrial dysfunctions are also critical to the pathogenesis of AD, contributing to the initiation and progression of this disease.[6] Aging is the major risk factor for AD, and the age of 65 years is often used to categorize it into early-onset AD (EOAD) and late-onset AD (LOAD). Although EOAD has a prominent genetic basis, LOAD has a more heterogeneous etiology that involves genetic risk and environmental factors, including infections.[7] Importantly, both EOAD and LOAD follow a similar pathological course, sharing the biochemical features mentioned above (doi:10.3233/JAD-143210). Although the understanding of the etiology and pathogenesis of AD has been expanded in the last years, the potential association between COVID-19 and AD remains unclear.[3] Importantly, some pathomechanisms related to AD are shared with COVID-19. The severity of COVID-19 neurological damage may be correlated with the innate and adaptive immune response to the virus and upon the existence of previous or concomitant CNS disease.[3] Thus, we identified differentially expressed genes from clinical datasets of COVID-19 patients, which were associated with AD (Figure 1), including several genes that encode potential biomarkers and/or whose expression have been altered in different samples from patients or in vitro and in vivo experimental models of AD.

Presenilins and cathepsin D are associated with EOAD because they regulate the cleavage of APP, leading to the formation of Aβ peptides.[8] *PSEN2*, *CTSD*, and *LGALS3* were upregulated in our analysis. *LGALS3* promotes Aβ oligomerization and toxicity in AD animal models, and it is increased in AD patients.[9] In contrast, membrane metalloendopeptidase and *ABCB1*, which participate in the degradation and clearance of Aβ,[8] were downregulated. Regarding *CHRNA7*, it was upregulated and has been increased in both neurons and astrocytes.[8]

We also identified upregulation of *IGFBP3* and *JAK2*. IGFBP3 can act as an inflammatory mediator and is highly increased in AD brains, in addition to possibly contribute to tau phosphorylation and cell death induced by Aβ,[10] while the JAK2/STAT3 pathway can modulate inflammatory responses and glial activation, indirectly regulating Aβ deposition and cognitive decline. *CTSL*, a proteinase that may be involved in immune system responses, was also upregulated and, interestingly, it is necessary for entry of the SARS-CoV-2 into the cell.[11] Although interferon-gamma participates in the inflammatory response, we found a downregulation of this gene, that can increase microglial activation and proinflammatory cytokines, but it also diminished phospho-tau pathology and increased neurogenesis in an animal model of AD.[12] Other genes related to immune pathways and that represent possible biomarkers for AD were also differentially expressed. AD is additionally linked to glucose and cholesterol metabolism, which presents an upregulation of genes related to glycolysis and synthesis and endocytosis of cholesterol. Moreover, we identified changes in the expression of genes that may be associated with responses to cellular energy levels and cellular stress, as well as neuronal cell death. Importantly, all these alterations can be found in both EOAD and LOAD.[13]

In summary, our data provided inputs/citations of biomarkers, gene expression, and posttranslational modifications,

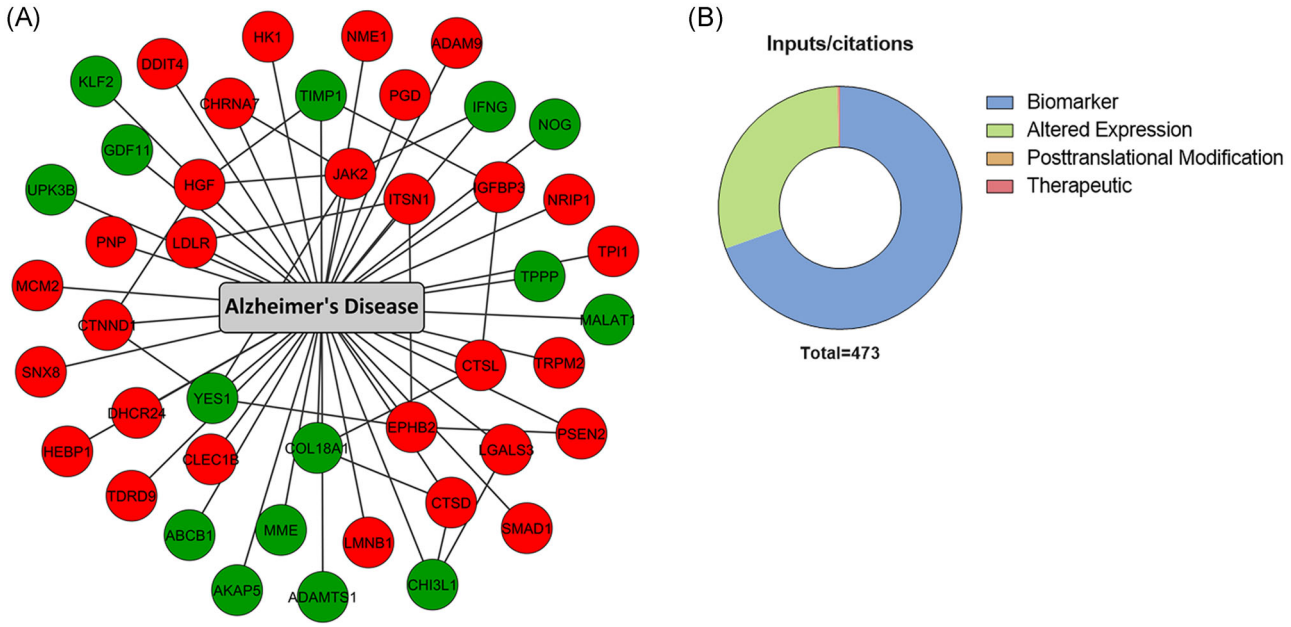

FIGURE 1 Alzheimer's disease (AD)-related markers in COVID-19 patients' blood samples. (A) Interactome of known and predicted protein-protein and gene-disease interactions of upregulated (red circle) and downregulated (green circle) gene-products differentially expressed in blood samples of COVID-19 patients found in SARSCOVIDB database[14] and limited to AD-related genes according to DisGeNET, visualized with Cytoscape v3.8.2 (cytoscape.org). (B) DisGeNET association type ontology of identified genes in "A" with AD. SARSCOVIDB is a platform that encompasses manually curate dysregulated genes in response to SARS-CoV-2 infection (sarscovidb.org). DisGeNET is a discovery platform containing one of the largest publicly available collections of genes and variants associated with human diseases (disgenet.org)

which were changed by COVID-19 and AD. Our findings also point out that patients with AD and COVID-19 may require the special attention of healthcare professionals to observe the late clinical outcomes of SARS-CoV-2 infection, because it can deteriorate or accelerate neurochemical dysfunctions, particularly associated with inflammation, metabolic disorders, and cellular homeostasis, which are crucial to the onset and progression of AD.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

André Quincozes-Santos, Larissa D. Bobermin, Lucélia Santi, and Walter O. Beys-da-Silva analyzed the data and wrote the manuscript. Rafael L. da Rosa and Emanuela F. Tureta analyzed the data. Walter O. Beys-da-Silva conceived the original idea and supervised the project.

DATA AVAILABILITY STATEMENT

All genes described in this Letter are available at SARSCOVIDB database (https://sarscovidb.org/).[14]

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