Short Communication

COVID-19 and Alzheimer's Disease, Closely Related?

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In this communication we discuss the possible link between neurodegenerative diseases and COVID-19, mainly in the etiopathogenic aspect, emphasizing microbiological and immune issues, resolving a possible interrelationship between both entities.

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Alzheimer's disease since its discovery has had various etiopathogenic currents, the most recent point to the infectious etiology of which some pathogens have stood out, such as viruses of the *Herpesviridae* family, mainly the *Herpes simplex virus* and the *Varicella virus. Zoster* (neurotropic par excellence) and some bacteria such as *Porphyromona gingivalis*, tend to stimulate the formation of beta-amyloid and Tau protein, which will ultimately trigger the disease.[1][2]

With the arrival of the COVID-19 pandemic, already in its fourth year of evolution, chronic-degenerative disorders have begun to be seen, such as the so-called Long COVID, in which there is chronic persistence of symptoms, beyond 12 weeks of having presented an acute picture, and with high involvement in the neuropsychiatric sphere in such a way that various symptoms of this nature have been detected. In this way, the Sar Cov2 virus, with a great affinity for the nervous system, has been shown to be able to affect said system and has been conferred on it to favor the appearance of Alzheimer's disease or exacerbate it in subjects with the disease, through the APO gene. This gene has an isoform called APO4, which is closely related to COVID-19 through the following mechanisms: At the cellular level, the APOE4 risk isoform confers high infectivity for the coronavirus; At the genetic level, APOE4 is associated with severe COVID-19; At the pathway level, the network connects APOE with COVID-19 risk factors such as ACE2, TMPRSS2, NRP1, and LZTFL1; behaviorally, APOE4-associated dementia may increase exposure to the coronavirus infection that causes COVID-19. [3]

 doi.org/10.32388/7HGPUJ

Another way in which there could be a relationship between these two entities is that Sars Cov2, specifically its S protein, has amyloidogenic potential, identifying seven amyloidogenic sequences in its structure; the seven isolated peptides met three criteria for amyloid fibrils: ThT nucleation-dependent polymerization kinetics, Congo red positivity, and ultrastructural fibrillar morphology. This amyloid material has been found in amyloid microthrombi that could travel and lodge in the central nervous system and start a process like tauopathies and probably at a systemic level with the subsequent risk of systemic amyloidosis. [4]

In severe COVID, it has become clear that anosmia is a serious symptom with a poor prognosis, (while dysgeusia has been associated with a better outcome in affected patients), and when its presence has been associated with COVID patients with the APOE4 gene, there is an increased risk of neurodegenerative dementia. This would be associated with chronic changes induced by the virus in the central nervous system. It is proposed that COVID-19 patients with anosmia and no other severe symptoms be followed up as part of studies specifically designed and approved to identify the early stages of dementia (especially LOAD and Dementia with Lewy Bodies).[5][6]

Another gene that could interact between these two entities is that of OAS1. Recently, oligoadenylate synthetase 1 (OAS1) was reported to contribute to Alzheimer's disease risk, by its enrichment in transcriptional networks expressed by microglia and the OAS1 variant, rs1131454, was confirmed to be associated with increased Alzheimer's disease risk. The same OAS1 locus has recently been associated with severe disease outcomes from COVID-19, linking the risk of both diseases. The single nucleotide polymorphisms rs1131454(A) and rs4766676(T) are associated with Alzheimer's disease, and rs10735079(A) and rs6489867(T) are associated with severe COVID-19, where the risk alleles are related to a decrease in the expression of OAS1. By analyzing single-cell RNA sequencing data from myeloid cells from Alzheimer's disease and COVID-19 patients, co-expression networks containing interferon (IFN)-responsive genes, including OAS1, were identified that significantly increase with age. and both diseases. [7]

In conclusion, there is a link between the genetic risk of Alzheimer's disease and susceptibility to severe disease from COVID-19 centered on OAS1 and APOE4, as well as protein S amyloidogenesis, findings with potential implications for future treatments for both Alzheimer's disease and COVID-19.

References

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Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.