

Letter to the Editor

OAS1 gene, Spike protein variants and persistent COVID-19-related anosmia: may the olfactory dysfunction be a harbinger of future neurodegenerative disease?

Dear Editor,

Magusali et al¹ recently reported a genetic link between risk for Alzheimer's disease (AD) and severe COVID-19 outcomes via the expression of the OAS1 gene. This is the first study investigating a genetic link between the two disorders.

Our letter aims to discuss the possible mechanisms underlying this finding and understand whether decreased expression of OAS1 might be linked to presence and persistence of anosmia in patients affected from COVID-19-related smell alteration. Magusali et al¹ identified four alleles adjacent to Oligoadenylate Synthetase 1 (OAS1) and OAS3 that might be responsible of the increased risk of developing AD and severe COVID-19. The authors identified that the upregulation of OAS1a triggers a pro-inflammatory state of microglia. OAS1 is involved in the regulation of cytokine expression, and it has been recently identified as a putative new risk gene for AD by a genome wide association study (GWAS). This GWAS has also identified the contribution of OAS1 gene to the genetic risk associated with critical outcomes of COVID-19. This gene expression is also involved in the interferon response. In the Magusali's study¹, the reduction of the expression of this gene induced differentiation of pluripotent stem cell to microglia; this excess of microglia could result in an exaggerated pro-inflammatory response when stimulated with IFN- γ ; at the same time the pro-inflammatory state of microglia produces pro-inflammatory cytokines that contribute to the perpetuation of the inflammatory response in the CNS. Magusali et al¹ showed that the regulation of this gene affects the microglia, and the regulation of these cells (activities and phenotype) is fundamental to balance the neuro-inflammation phenomena. The latter might be the link between Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection and long-term neurological sequela.

We hypothesized that the inflammation of the olfactory bulbs (OBs)², which causes the onset of anosmia in patients who suffers from less-severe form of COVID-19^{3,4}, might be a sign that heralds the development of long-term neurological concerns especially in those subjects who suffered from persistent smell alteration. Cadaveric studies^{5,6} have shown the presence of microglia into the OBs of patients with COVID-19 and alterations of the smell; these cells normally represent the immune response to limit the spread and the penetration of the virus to other part of the brain^{7,8}. However, despite quite common, this symptom is not present in all patients and, more important does not persist more than few months (< 3) in the majority of the cases⁹. However, in a minority of patients, about 20%, it persists longer, and can become disabling¹⁰. We questioned whether this genetic link¹ alone could explain the difference in the onset, severity, persistence, or resolution of the smell alterations or spike variants should be considered.

Bouayed and Bohn⁷ suggested that the heterogeneity of the host reaction to SARS-CoV-2 infection may reflect differences in activation of microglia, the cells that protect the brain from viral entry⁸. Magusali et al¹ identified in the OAS1 gene the link that might explain the presence of pro-inflammatory microglia in case of COVID-19 severe infection. Since microglia have been identified in the OBs¹¹, we speculate that i) this gene might be linked to the presence, progression, and persistence of anosmia, and ii) the presence of this symptom be a harbinger of future neurodegenerative disease as AD.

The Spike protein is the main trigger of the neuroinflammatory events observed in SARS-CoV-2 infection¹² and can cross the blood-brain-barrier (ACE2 and TMPRSS2 BBB). Once in the brain, SARS-

CoV-2 induces massive inflammation, activating microglia through TLR2-dependent activation of NF- κ B pathway. Spike subproteins (S1 and S2) induce production of pro-inflammatory cytokines IL-6, TNF α , and IL-1 β (S2 more potently than S1) in the periphery (blood-macrophages) and in the microglia of the CNS. The presence of pro-inflammatory cytokines induces the increase of pro-inflammatory microglia phenotype, which, in patients who present with low levels of OAS1, might be massive and results in extensive synaptic damage with consequent loss of smell. As Magusali et al¹ showed the interaction between the expression of this gene and microglia as plausible link between AD and COVID-19, we hypothesize that his concept might also incorporate the alteration of the smell. In fact, smell disorders have been identified as one of the earliest symptoms of AD¹³, and in both diseases (COVID-19 and AD) neuro-inflammation and neurodegeneration play a key role¹⁴. On the other hand, the response to the inflammatory event and the modulation of neuroinflammation are strongly correlated with the genetic profiles of affected patients¹⁵. These genetic risk factors correlate with the resolution or persistence of the inflammatory processes inside and outside the brain¹⁵.

Magusali's study¹ was focused on the genetic profile of the host, but we think that also the variants of Spike proteins should be further investigated, taking into consideration the variable severity of COVID-19. In fact, different Spike proteins combined with different genetic susceptibility of the host to its inflammatory effects, might play a role in determining the severity of infection, both in the systemic and localized form. The same mechanism could also explain the difference in the prevalence and persistence of the olfactory disorders, given that anosmia starts from olfactory bulbs infection and consequent inflammation³. The interaction between the genetics of the host and the virus, the ability to modulate the inflammation both at local (nose) and systemic level of the host, as well as their predisposition to neuro-inflammation, might all explain the reason why some patients have long-lasting smell disorders. Long-term observational studies on patients with persistent olfactory problems would be necessary to understand whether the smell alteration might be a harbinger of neurodegenerative disease. In this unlucky occurrence, we should consider SARS-CoV-2-related neurodegenerative diseases.

If persistent post-COVID-19 anosmia might be related to the presence of OAS1 in the patients, an early treatment with anti-inflammatory agents as well as modulators of the microglia response^{10,16} might prevent the development of a neurodegenerative disease (Figure 1). Further, prospective studies are needed to confirm these findings and to shed more light on our hypothesis.

Authors' Contributions

Conceptualization and study design: ADS; Literature review: ADS, CS, and MJB; Supervision: CA; Reading of selected articles: Neurology: EB, CS and CA, Otolaryngology: ADS, MR and MJB, Biology/Neuroscience: ADS and CA; Definition of conclusions: ADS, CA, MJB, CS and EB; Article writing (first draft): ADS; Criticism and review: MJB, MR, CS EB, CA; Article writing (definitive version): All authors.

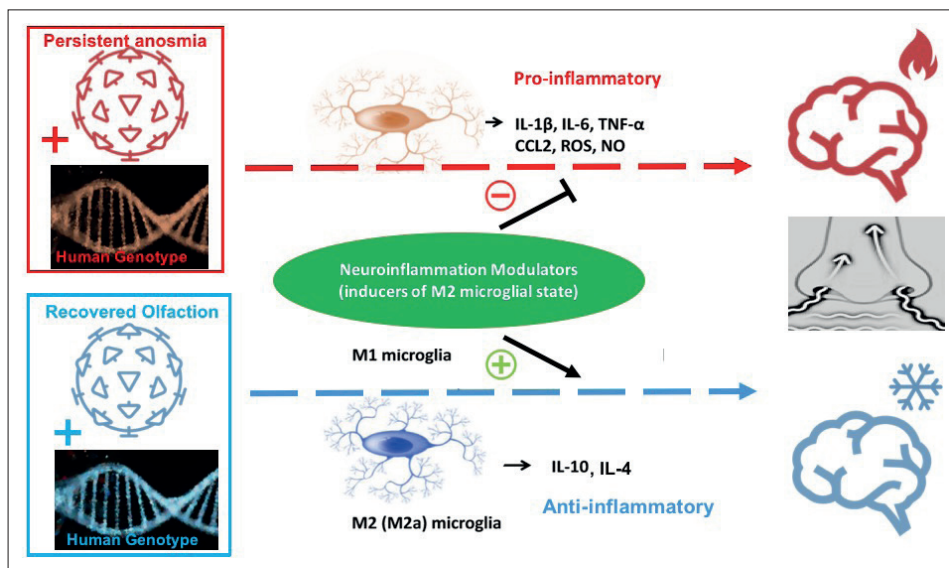


Figure 1. Proposed role of neuroinflammation and inflammatory modulators in clinical course of COVID-19 anosmia. A patient's susceptibility profile may interact with viral infection to influence prognosis. Shifting microglial transitions anti-inflammatory microglia state with modulators may reduce neuroinflammation, thereby reducing synaptic injury and risk of persistent anosmia.

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Conflict of interest

The authors declare that they have no conflict of interest.

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