Molecular mimicry in the post-COVID-19 signs and symptoms of neurovegetative disorders?

Many individuals who have severe forms of COVID-19 experience a suite of neurovegetative signs and symptoms (eg, tachycardia) after their recovery, suggesting that the imbalance of the sympathetic-parasympathetic activity of the autonomic nervous system[1] could continue for many weeks or months after respiratory symptoms stop. Moreover, a reduction of the parasympathetic tone could have a role in restricting the cholinergic anti-inflammatory pathway, thus favouring hyperinflammation and cytokine storm in the most severe phases of the disease.

As reported by Guglielmo Lucchese in *The Lancet Microbe*,[2] SARS-CoV-2 can damage the nervous system via an indirect mechanism, resulting in a high prevalence of autoantibodies, mainly against unknown autoantigens in the brain, in cerebrospinal fluid from patients with neurological complications.[2] The cause of low vagal tone and SARS-CoV-2 has not yet been investigated sufficiently and here we would like to share some original data supporting the putative role of molecular mimicry as the culprit of COVID-19 pathogenesis, including the post-COVID-19 neurovegetative syndrome.[2–5]

Using methods that have been previously described,[3] we looked specifically at the human proteins expressed in vagal nuclei and ganglia. As shown in the appendix (pp 1–2), we found that 22 of these proteins share peptides that could putatively generate a T-cell or B-cell driven autoimmune response. The location and function of these proteins are described in the appendix (pp 3–24).

Fibres of the vagal nerve originate from four nuclei located in the medulla oblongata—ie, the dorsal motor nucleus, the nucleus ambiguus, the solitary nucleus, and, to a lesser extent, the spinal trigeminal nucleus. These fibres contribute to the somatic and visceral motricity, somatic and visceral sensibility, and the sense of taste.

The visceral motor inputs originate specifically from the dorsal motor nucleus and nucleus ambiguus and are directed towards the heart, the airways, and the gastrointestinal system. Moreover, the vagal visceral innervation includes two sensory ganglia of the peripheral nervous system—the nodose ganglion and the jugular ganglion. In particular, peripheral fibres of the neurons of the nodose ganglion not only innervate the taste buds on the epiglottis, the chemoreceptors of the aortic bodies, and baroreceptors in the aortic arch, but they also provide sensory innervation to the circulatory, respiratory, and gastrointestinal systems. An impairment of the vagal innervation of the heart can lead to tachycardia at rest, which is often seen by clinicians during physical examination of patients who have recovered from a severe form of COVID-19.[1]

We found that the dorsal motor nucleus, nucleus ambiguus, nodose ganglion, and jugular ganglion can all host neurons presenting proteins with epitopes in common with SARS-CoV-2 proteins, and the peptide TGRLQSL is embedded in one immunoreactive linear epitope that has already been experimentally validated in the human host (Immune Epitope Database and Analysis Resource identification number 36724) to be able to generate an autoimmune response.

We share our findings to prompt further studies assessing whether severe forms of COVID-19 could produce transitory or permanent damage in some vagal structure and whether this can, in turn, be responsible for the low vagal tone and the related clinical signs and symptoms.

We declare no competing interests.

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See **Online** for appendix

For the **epitope summary of TGRLQSL** see https://www.iedb.org/epitope/36724