Long/post-COVID, evidently represents a heterogeneous nosological entity, despite the existence of similar or overlapping symptoms between patients, and clear diagnostic criteria are yet to be established. Multiple organ systems are affected, including the respiratory, cardiovascular, nervous, and gastrointestinal systems. In this study, the authors from Spain and Costa Rica investigated corneal innervation in individuals with persistent symptoms of long COVID more than 20 months after acute infection.

The cornea is one of the most innervated tissues, receiving heterogeneous sensory nerves from the ophthalmic branch of the trigeminal nerve and a small number of autonomic sympathetic nerve fibers from the superior cervical ganglion cell bodies. Its basal epithelium is populated by resident immune cells, known as dendritic cells, which bridge the innate and adaptive immune responses, and contribute to corneal nerve homeostasis.

Corneal confocal microscopy is a noninvasive imaging technique for direct visualization of corneal structure *in vivo*, including the corneal subbasal nerve plexus. The loss of corneal nerve fibers is indicative of neurodegeneration and may be associated with various diseases. Due to this reason, *in vivo* confocal microscopy has been used to identify small-fiber neuropathy in immune-mediated small-fiber neuropathies and peripheral neuropathies.

Previous investigations have reported a decrease in corneal nerve fibers and an increase in

dendritic cells in acute COVID-19 patients and individuals diagnosed with long COVID 3–4 months after the acute infection. Previous data have also shown that COVID-19 vaccination increased dendritic cells in the cornea, which may enhance local immune response.

Recent studies have associated long COVID syndrome with small-fiber neuropathy, characterized by a selective alteration of small, thinly myelinated nerve fibers such as A-fibers, and unmyelinated C-fibers. Small-fiber neuropathy affects both sensory and autonomic nerves.
https://discovermednews.com/dysautonomia-and-neuropathy-in-small-fiber-neuropathy-after-covid-19/

About the study

The diagnosis of long COVID syndrome was based on the WHO criteria. Individuals with eye diseases, such as ocular surface disease and glaucoma, with a history of systemic disease before infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), contact lens wearers, and individuals who had undergone eye surgery within the last six months were excluded. The control group consisted of volunteers who did not wear contact lenses and did not have any systemic or eye diseases. Participants in both groups were older than 18 years.

Corneal confocal microscopy (with the Heidelberg Retina Tomograph II) was used to visualize morphological parameters of the subbasal nerve plexus, including corneal nerve fiber density (number of nerve fibers *per* square millimeter), nerve fiber length (total length of nerves in millimeters *per* square millimeter), nerve branch density (number of primary branch points on the main nerve fibers *per* square millimeter), and nerve fiber total branch density (total number of branch points *per* square millimeter). Other morphological changes in nerve fibers, including microneuromas, were also detected. The dendritic cells in the subbasal nerve plexus were numbered by hand using specialized software. The density of dendritic cells was also calculated (cells/mm2).

Results

This descriptive cross-sectional study enrolled 88 individuals, 60 diagnosed with long COVID, and 28 controls. 78% (47 individuals) of patients diagnosed with long COVID

syndrome were vaccinated.

Corneal confocal microscopy revealed differences in corneal innervation between patients with long COVID and the controls. Compared to the control group, patients with long COVID had significantly lower corneal nerve fiber densities, shorter nerve fiber lengths, and lower densities of nerve fiber branches. Microneuromas were found in 15% of patients diagnosed with long COVID syndrome.

Patients with long COVID also had a higher density and a larger area of corneal dendritic cells, which could potentially enhance the local immune response. According to the authors, this immunological response may contribute to the corneal nerve degeneration observed in long COVID patients.

Conclusion

This study has revealed reduced corneal innervation, including a decreased corneal nerve fiber density, nerve fiber length, and nerve branch density, and a higher density and a larger area of corneal dendritic cells, in individuals diagnosed with long COVID syndrome more than 20 months after the acute infection. The authors noted that the pathophysiological basis for these findings is unclear, but, the results support the hypothesis that neuroinflammation is one of the persistent complications in long COVID syndrome.

These results also highlighted the potential role of corneal confocal microscopy as an effective non-invasive diagnostic procedure in patients with long COVID syndrome.

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