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- 1 The CRASH-3 trial collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. *Lancet* 2019; **394**: 1713–23.
- 2 Roberts I, Yates D, Sandercock P, et al. Effect of intravenous corticosteroids on death within 14 days in 10 008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet* 2004; **364**: 1321–28.
- 3 Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. *Nature* 2019; **567**: 305–07.
- 4 Roberts I, Prieto-Merino D, Manno D. Mechanism of action of tranexamic acid in bleeding trauma patients: an exploratory analysis of data from the CRASH-2 trial. *Crit Care* 2014; **18**: 685.
- 5 CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010; **376**: 23–32.
- 6 Brenner A, Arribas M, Cuzick J, et al. Outcome measures in clinical trials of treatments for acute severe haemorrhage. *Trials* 2018; **19**: 533.

See Online for appendix



## Inflammatory olfactory neuropathy in two patients with COVID-19

Published Online  
July 10, 2020

[https://doi.org/10.1016/S0140-6736\(20\)31525-7](https://doi.org/10.1016/S0140-6736(20)31525-7)

We report two cases of olfactory neuropathy diagnosed at autopsy in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. One patient experienced anosmia. Information about anosmia was not available in the other patient.

Patient 1, a man aged 70 years, and patient 2, a man aged 79 years, both tested positive for SARS-CoV-2. Patient 1 was a renal transplant recipient with coronary artery disease and arterial hypertension. He developed progressive respiratory failure due to COVID-19 pneumonia and required mechanical ventilation. He was treated with hydroxychloroquine (total 1600 mg). Patient 2 was previously diagnosed with severe pulmonary hypertension and was admitted with fever, cough, and increasing dyspnoea as well as loss of taste and smell. He was also treated with hydroxychloroquine

(total 1600 mg); however, he declined invasive treatment. Patient 1 died 8 days after hospital admission; patient 2 died 6 days after hospital admission.

Patient consent for research was obtained from both patients. Post-mortem histological analysis of the olfactory epithelium in both patients showed prominent leukocytic infiltrates in the lamina propria and focal atrophy of the mucosa. The histological analysis of olfactory epithelium from both patients is in the appendix. We found a slight predominance of CD3-positive T cells over CD20-positive B lymphocytes. Expectedly, olfactory nerve fibres in the lamina propria were negative for myelin basic protein. However, they showed so-called digestion chambers, which stained positive for CD68 on immunohistochemistry, suggestive of axonal damage. Scattered CD45-positive leukocytes were consistent with an inflammatory neuropathy; the infiltrates comprised both CD4-positive and CD8-positive T lymphocytes. CD20 staining was negative. In both patients, the olfactory tracts showed few isolated CD45-positive infiltrates; the olfactory striae were unremarkable. Both brains showed perivascular leukocytic infiltrates, predominantly in the basal ganglia and intravascular microthrombi.

Anosmia is a common symptom in patients with COVID-19.<sup>1</sup> Inflammation of the olfactory system and anosmia have been reported in other viral diseases,<sup>2</sup> as was age-related atrophy of the olfactory epithelium.<sup>3</sup> The observed neuritis is most likely associated with axonal damage, as olfactory fila lack myelin.<sup>4</sup> Consistent with previous reports, the olfactory tracts were largely unremarkable, except for a few endoneurial leukocytes in both patients.<sup>5</sup> SARS-CoV-2-induced damage might be mediated by viral entry through its receptor angiotensin converting enzyme 2 and the transmembrane serine protease 2, which are expressed in non-neural cells of the olfactory epithelium.<sup>6</sup> It is unclear whether the observed inflammatory

neuropathy is a result of direct viral damage or is mediated by damage to supporting non-neural cells. Due to the rapidly evolving pandemic, unravelling the neuroinvasive properties of SARS-CoV-2 will have major implications for patients with COVID-19.

PS, AA, and KF contributed equally. SU reports grants from Swiss National Science Foundation, Zurich Lung, and Orpha Swiss; and personal fees from Actelion and MSD, outside of the submitted work. TH reports grants from aspruclip, Sony, the Smell and Taste Lab, and Takasago, outside of the submitted work. All other authors declare no competing interests. We thank Daniela Meir and Fabian Baron for technical assistance.

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- 1 Levinson R, Elbaz M, Ben-Ami R, et al. Anosmia and dysgeusia in patients with mild SARS-CoV-2 infection. *medRxiv* 2020; published online April 14. <https://doi.org/10.1101/2020.04.11.20055483> (preprint).
- 2 van Riel D, Verdijk R, Kuiken T. The olfactory nerve: a shortcut for influenza and other viral diseases into the central nervous system. *J Pathol* 2015; **235**: 277–87.
- 3 Attems J, Walker L, Jellinger KA. Olfaction and aging: a mini-review. *Gerontology* 2015; **61**: 485–90.
- 4 Garcia-Gonzalez D, Murcia-Belmonte V, Clemente D, De Castro F. Olfactory system and demyelination. *Anat Rec (Hoboken)* 2013; **296**: 1424–34.
- 5 Solomon IH, Normandin E, Bhattacharyya S, et al. Neuropathological features of Covid-19. *N Engl J Med* 2020; published online June 12. <https://doi.org/10.1056/NEJMc2019373>.
- 6 Ziegler CGK, Allon SJ, Nyquist SK, et al. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. *Cell* 2020; **181**: 1016–35.