Patologie onemocnění COVID-19

mýty a fakta

Radoslav Matěj

Ústav patologie a molekulární medicíny 3.LF UK a Thomayerovy nemocnice

Ústav patologie 3. LF UK a Fakultní nemocnice Královské Vinohrady

1 Cite Share

Phage therapy for secondary bacterial infections with **COVID-19**.

Wu N, Chen LK, Zhu T.

Curr Opin Virol. 2021 Nov 9;52:9-14. doi: 10.1016/j.coviro.2021.11.001. Online ahead of print.

PMID: 34800893 Review.

With more than 200 million people affected and 4.5 million deaths so far, the coronavirus disease 2019 (**COVID-19**) pandemic has become one of the greatest disasters in human history. ...As natural killers of bacteria, phages are recognized as promising alternatives t ...

2 Cite Share

The **COVID-19** Patient in the Surgical Intensive Care Unit.

Monroe I, Dale M, Schwabe M, Schenkel R, Schenarts PJ.

Surg Clin North Am. 2022 Feb;102(1):1-21. doi: 10.1016/j.suc.2021.09.015. Epub 2021 Sep 29.

PMID: 34800379 Review.

Although **COVID-19** is primarily a respiratory disease, it is also associated with significant **pathology** in the brain, heart, vasculature, lungs, gastrointestinal tract, and kidneys. This article provides an overview of **COVID-19** using an organ-bas ...

3 Cite Share

[Manifestation of SARS-CoV-2 **infection** on oral mouth mucosa].

Laskowska E, Radwan-Oczkoa M.

Pol Merkur Lekarski. 2021 Oct 22;49(293):374-378.

PMID: 34800028 Review. Polish.

These lesions seem to be very important because they are seen in various clinical presentation and should be taken into consideration in the **COVID-19** diagnosis.A lot of changes and oral mucosal lesions

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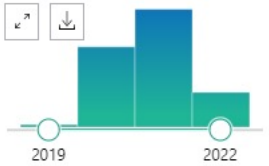

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Ad interim recommendations for diagnosing SARS-CoV-2 **infection** by the IFCC SARS-CoV-2 variants working group.

Lippi G, Favresse J, Gromiha MM, SoRelle JA, Plebani M, Henry BM.

Clin Chem Lab Med. 2022 Apr 22. doi: 10.1515/cclm-2022-0345. Online ahead of print.

PMID: 35452576

This document, endorsed by the IFCC Working Group on SARS-CoV-2 Variants, aims to update previous indications for diagnosing acute SARS-CoV-2 **infection**, taking into consideration the evidence that has emerged after the origin and spread of new lineages and sub-lineages of ...

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The challenge of SARS-CoV-2 environmental monitoring in schools using floors and portable HEPA filtration units: Fresh or relic RNA?

Zuniga-Montanez R, Coil DA, Eisen JA, Pechacek R, Guerrero RG, Kim M, Shapiro K, Bischel HN.

PLoS One. 2022 Apr 22;17(4):e0267212. doi: 10.1371/journal.pone.0267212. eCollection 2022.

PMID: 35452479

Testing surfaces in school classrooms for the presence of SARS-CoV-2, the virus that causes **COVID-19**, can provide public-health information that complements clinical testing. ...However, no confirmed **COVID-19** cases were identified among students associ ...

3 Cite Share

Blood utilization and quality indicators at a university hospital in the Eastern Province of Saudi Arabia.

Shash H, Alabdulqader R, Alshehri L, Alkathery N, Al-Abdulrahman R, Alahmed S, Bubshait D, AlKhater S, Al-Nafie A.

PLoS One. 2022 Apr 22;17(4):e0267449. doi: 10.1371/journal.pone.0267449. eCollection 2022.

PMID: 35452477

The donations gradually increased over the years, peaking just before **COVID-19** pandemic started in

Existuje jednoznačně diagnosticky specifický histopatologický obraz nemoci COVID-19?

NE!

... i když možná

Virchows Archiv
https://doi.org/10.1007/s00428-022-03319-2

REVIEW AND PERSPECTIVES

Organ manifestations of COVID-19: what have we learned so far (not only) from autopsies?

Danny Jonigk[1] · Christopher Werlein[1] · Till Acker[2] · Martin Aepfelbacher[3] · Kerstin U. Amann[4] · Gustavo Baretton[5] · Peter Barth[6] · Rainer M. Bohle[7] · Andreas Büttner[8] · Reinhard Büttner[9] · Reinhard Dettmeyer[10] · Philip Eichhorn[11] · Sefer Elezkurtaj[12] · Irene Esposito[13] · Katja Evert[14] · Matthias Evert[14] · Falko Fend[15] · Nikolaus Gaßler[16] · Stefan Gattenlöhner[17] · Markus Glatzel[18] · Heike Göbel[9] · Elise Gradhand[19] · Torsten Hansen[20] · Arndt Hartmann[11] · Axel Heinemann[21] · Frank L. Heppner[22,23,24] · Julia Hilsenbeck[5] · David Horst[12] · Jan C. Kamp[25] · Gita Mall[26] · Bruno Märkl[27] · Benjamin Ondruschka[28] · Jessica Pablik[5] · Susanne Pfefferle[3] · Alexander Quaas[9] · Helena Radbruch[22] · Christoph Röcken[29] · Andreas Rosenwald[30] · Wilfried Roth[31] · Martina Rudelius[32] · Peter Schirmacher[33] · Julia Slotta-Huspenina[34] · Kevin Smith[19] · Linna Sommer[5] · Konrad Stock[35] · Philipp Ströbel[36] · Stephanie Strobl[31] · Ulf Titze[20] · Gregor Weirich[34] · Joachim Weis[37] · Martin Werner[38] · Claudia Wickenhauser[39] · Thorsten Wiech[40] · Peter Wild[19] · Tobias Welte[25] · Saskia von Stillfried[41] · Peter Boor[41,42]

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Abstract

The use of autopsies in medicine has been declining. The COVID-19 pandemic has documented and rejuvenated the importance of autopsies as a tool of modern medicine. In this review, we discuss the various autopsy techniques, the applicability of modern analytical methods to understand the pathophysiology of COVID-19, the major pathological organ findings, limitations or current studies, and open questions. This article summarizes published literature and the consented experience of the nationwide network of clinical, neuro-, and forensic pathologists from 27 German autopsy centers with more than 1200 COVID-19 autopsies. The autopsy tissues revealed that SARS-CoV-2 can be found in virtually all human organs and tissues, and the majority of cells. Autopsies have revealed the organ and tissue tropism of SARS-CoV-2, and the morphological features of COVID-19. This is characterized by diffuse alveolar damage, combined with angiocentric disease, which in turn is characterized by endothelial dysfunction, vascular inflammation, (micro-) thrombosis, vasoconstriction, and intussusceptive angiogenesis. These findings explained the increased pulmonary resistance in COVID-19 and supported the recommendations for antithrombotic treatment in COVID-19. In contrast, in extra-respiratory organs, pathological changes are often nonspecific and unclear to which extent these changes are due to direct infection vs. indirect/secondary mechanisms of organ injury, or a combination thereof. Ongoing research using autopsies aims at answering questions on disease mechanisms, e.g., focusing on variants of concern, and future challenges, such as post-COVID conditions. Autopsies are an invaluable tool in medicine and national and international interdisciplinary collaborative autopsy-based research initiatives are essential.

Keywords SARS-CoV-2 · Diffuse alveolar damage · Acute kidney damage · Immune response

Histopathology

Histopathology 2020, **77**, 570–578. DOI: 10.1111/his.14180

Diffuse alveolar damage (DAD) resulting from coronavirus disease 2019 Infection is Morphologically Indistinguishable from Other Causes of DAD

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Konopka K E, Nguyen T, Jentzen J M, Rayes O, Schmidt C J, Wilson A M, Farver C F & Myers J L. (2020) *Histopathology* **77**, 570–578. https://doi.org/10.1111/his.14180

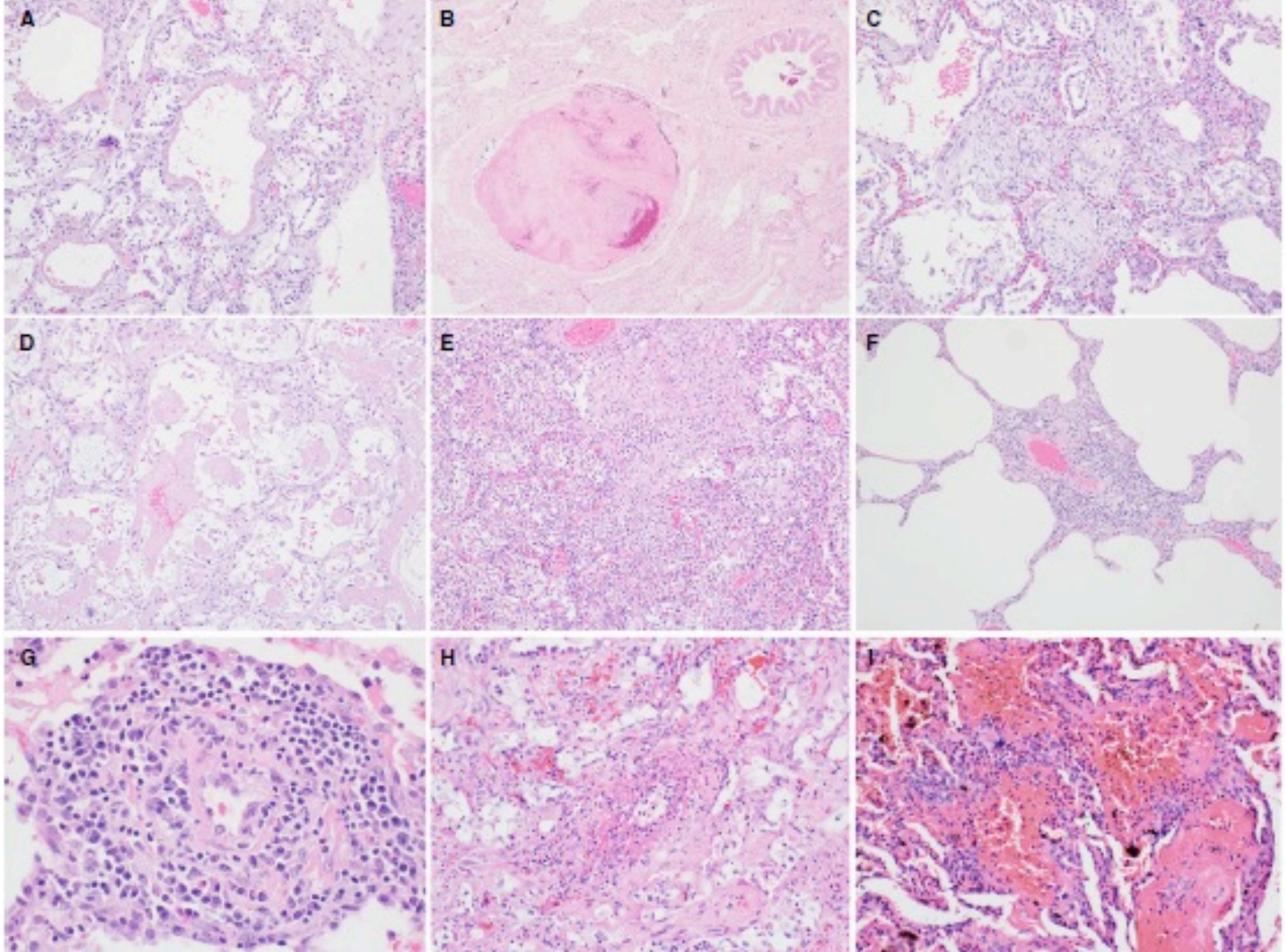
Diffuse alveolar damage (DAD) resulting from coronavirus disease 2019 Infection is Morphologically Indistinguishable from Other Causes of DAD

Aims: Diffuse alveolar damage (DAD) is a ubiquitous finding in inpatient coronavirus disease 2019 (COVID-19)-related deaths, but recent reports have also described additional atypical findings, including vascular changes. An aim of this study was to assess lung autopsy findings in COVID-19 inpatients, and in untreated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive individuals who died in the community, in order to understand the relative impact of medical intervention on lung histology. Additionally, we aimed to investigate whether COVID-19 represents a unique histological variant of DAD by comparing the pathological findings with those of uninfected control patients.

Methods and results: Lung sections from autopsy cases were reviewed by three pulmonary pathologists, including two who were blinded to patient cohort. The cohorts included four COVID-19 inpatients, four cases with postmortem SARS-CoV-2 diagnoses who died in the community, and eight SARS-CoV-2-negative control cases. DAD was present in all but one SARS-CoV-2-positive patient, who was asymptomatic and died in the community. Although SARS-CoV-2-positive patients were noted to have more focal perivascular inflammation/endothelialitis than control patients, there were no significant differences in the presence of hyaline membranes, fibrin thrombi, airspace organisation, and 'acute fibrinous and organising pneumonia'-like intra-alveolar fibrin deposition between the cohorts. Fibrinoid vessel wall necrosis, haemorrhage and capillaritis were not features of COVID-19-related DAD.

Conclusions: DAD is the primary histological manifestation of severe lung disease in COVID-19 patients who die both in hospital and in the community, suggesting no contribution of hyperoxaemic mechanical ventilation to the histological changes. There are no distinctive morphological features with which to confidently differentiate COVID-19-related DAD from DAD due to other causes.

Keywords: autopsy, COVID, diffuse alveolar damage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Histopathology

Histopathology 2020, 77, 198–209. DOI: 10.1111/his.14134

Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction

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Menter T, Haslbauer J D, Nienhold R, Savic S, Hopfer H, Deigendesch N, Frank S, Turek D, Willi N, Pargger H, Bassetti S, Leuppi J D, Cathomas G, Tolnay M, Mertz K D & Tzankov A.
(2020) *Histopathology* 77, 198–209. https://doi.org/10.1111/his.14134

Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction

Aims: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly evolved into a sweeping pandemic. Its major manifestation is in the respiratory tract, and the general extent of organ involvement and the microscopic changes in the lungs remain insufficiently characterised. Autopsies are essential to elucidate COVID-19-associated organ alterations.

Methods and results: This article reports the autopsy findings of 21 COVID-19 patients hospitalised at the University Hospital Basel and at the Cantonal Hospital Baselland, Switzerland. An *in-corpore* technique was performed to ensure optimal staff safety. The primary cause of death was respiratory failure with exudative diffuse alveolar damage and massive capillary congestion, often accompanied by microthrombi despite anticoagulation. Ten cases showed superimposed bronchopneumonia. Further findings included pulmonary embolism ($n = 4$), alveolar haemorrhage ($n = 3$), and vasculitis ($n = 1$). Pathologies in other organ systems were predominantly attributable to shock; three patients showed signs of generalised and five of pulmonary thrombotic microangiopathy. Six patients were diagnosed with senile cardiac amyloidosis upon autopsy. Most patients suffered from one or more comorbidities (hypertension, obesity, cardiovascular diseases, and diabetes mellitus). Additionally, there was an overall predominance of males and individuals with blood group A (81% and 65%, respectively). All relevant histological slides are linked as open-source scans in supplementary files.

Conclusions: This study provides an overview of postmortem findings in COVID-19 cases, implying that hypertensive, elderly, obese, male individuals with severe cardiovascular comorbidities as well as those with blood group A may have a lower threshold of tolerance for COVID-19. This provides a pathophysiological explanation for higher mortality rates among these patients.

Keywords: autopsy, cardiovascular, lung, SARS-CoV-2, COVID-19, senile amyloidosis, kidney

Table 2. Summary of autopsy findings

Organ	Diagnosis	*n*	%
Lung	Pulmonary capillary congestion	21/21	100
	DAD, exudative	16/21	76
	DAD, proliferative	8/21	38
	Reactive pneumocytes and syncytial cells	11/21	52
	Microthrombi of alveolar capillaries	5/11	45
	Bronchopneumonia, diffuse	6/21	29
	Bronchopneumonia, focal	4/21	19
	Severe mucous tracheitis	6/21	29
	Emphysema	6/21	29
	Pulmonary embolism	4/21	19
	Prominent lymphoid infiltrates	3/21	14
	Pulmonary haemorrhage	3/21	14
	Amyloidosis of pulmonary vessels	3/21	14
	Vasculitis	1/21	5
Heart	Myocardial hypertrophy	15/21	71
	Senile amyloidosis	6/21	29
	Peracute myocardial cell necrosis	3/21	14
	Acute myocardial infarction	1/21	5
Kidney	Acute tubular damage	14/15	93
	Disseminated intravascular coagulation	3/17	18
	Hypertensive nephropathy	2/17	12
	Diabetic nephropathy	2/17	12
Liver	Steatosis	7/17	41
	Shock necrosis	5/17	29
	ASH/NASH	3/17	18
Lymph node	Increased presence of plasmablasts	5/9	56
	Congestion	6/9	67
Spleen	Acute splenitis	6/21	29
Bone marrow	Reactive left shift of myelopoiesis	3/5	60
	Involvement by haematopoietic malignancies	2/5	40

ASH, alcoholic steatohepatitis; DAD, diffuse alveolar damage; NASH, non-alcoholic steatohepatitis.

ESC European Society of Cardiology

European Heart Journal (2020) **41**, 3827–3835
doi:10.1093/eurheartj/ehaa664

CLINICAL RESEARCH
Heart failure

Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study

Cristina Basso [1†], Ornella Leone [2†], Stefania Rizzo [1], Monica De Gaspari[1], Allard C. van der Wal[3], Marie-Christine Aubry[4], Melanie C. Bois [4], Peter T. Lin [4], Joseph J. Maleszewski [4], and James R. Stone [5*]

[1]Cardiovascular Pathology, Azienda Ospedaliera, Department of Cardiac, Thoracic and Vascular Sciences and Public Health, University of Padua, Padua, Italy; [2]Cardiovascular and Cardiac Transplant Pathology Unit, Department of Pathology, Sant'Orsola-Malpighi University Hospital, Bologna, Italy; [3]Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands; [4]Department of Pathology, Mayo Clinic, Rochester, MN, USA; and [5]Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

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See page 3836 for the editorial comment on this article (doi: 10.1093/eurheartj/ehaa727)

Aims Coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been associated with cardiovascular features of myocardial involvement including elevated serum troponin levels and acute heart failure with reduced ejection fraction. The cardiac pathological changes in these patients with COVID-19 have yet to be well described.

Methods and results In an international multicentre study, cardiac tissue from the autopsies of 21 consecutive COVID-19 patients was assessed by cardiovascular pathologists. The presence of myocarditis, as defined by the presence of multiple foci of inflammation with associated myocyte injury, was determined, and the inflammatory cell composition analysed by immunohistochemistry. Other forms of acute myocyte injury and inflammation were also described, as well as coronary artery, endocardium, and pericardium involvement. Lymphocytic myocarditis was present in 3 (14%) of the cases. In two of these cases, the T lymphocytes were CD4 predominant and in one case the T lymphocytes were CD8 predominant. Increased interstitial macrophage infiltration was present in 18 (86%) of the cases. A mild pericarditis was present in four cases. Acute myocyte injury in the right ventricle, most probably due to strain/overload, was present in four cases. There was a non-significant trend toward higher serum troponin levels in the patients with myocarditis compared with those without myocarditis. Disrupted coronary artery plaques, coronary artery aneurysms, and large pulmonary emboli were not identified.

Conclusions In SARS-CoV-2 there are increased interstitial macrophages in a majority of the cases and multifocal lymphocytic myocarditis in a small fraction of the cases. Other forms of myocardial injury are also present in these patients. The macrophage infiltration may reflect underlying diseases rather than COVID-19.

Keywords Myocarditis • Macrophages • COVID-19 • SARS • SARS-CoV-2 • Heart • Myocardium • Autopsy

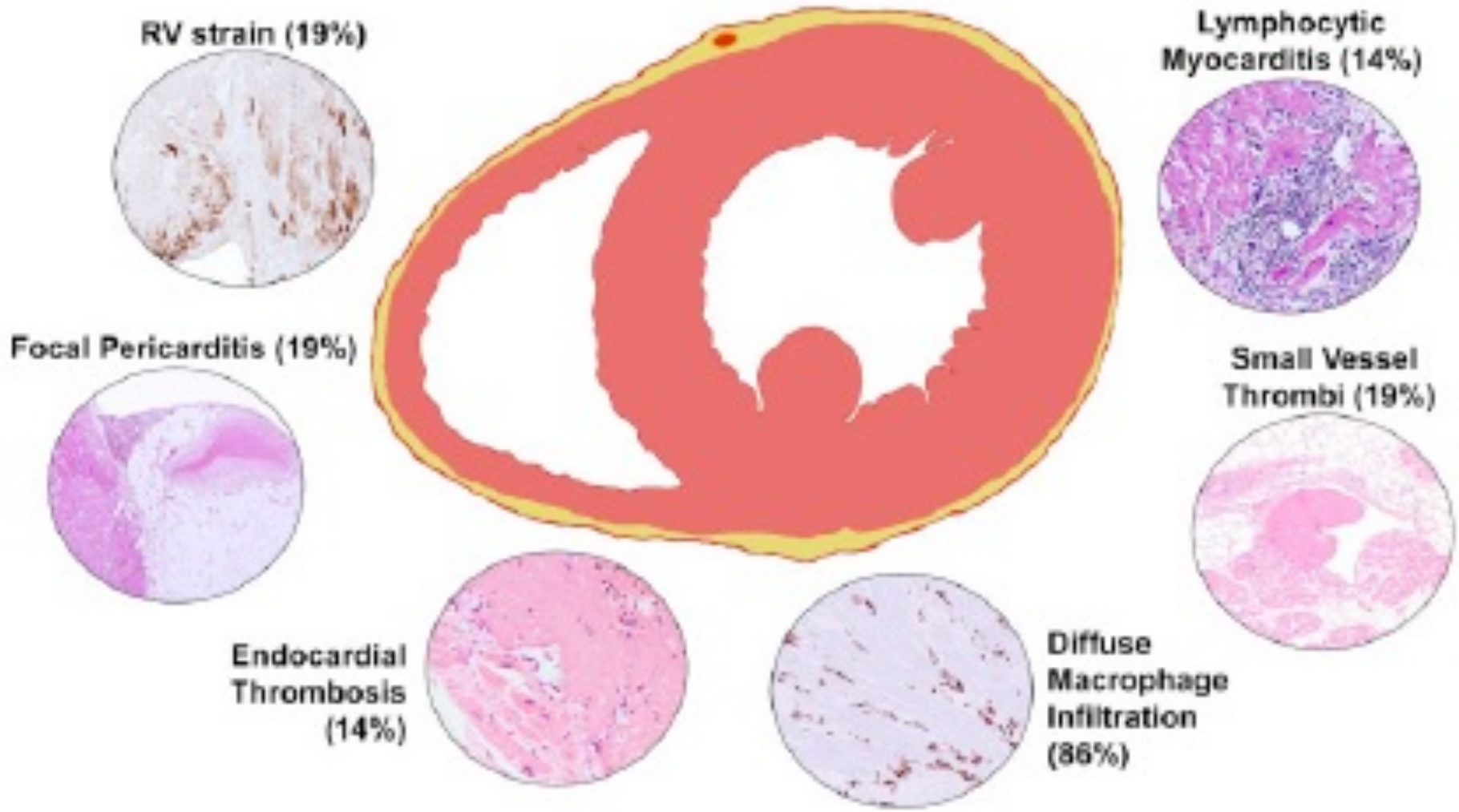

Figure 7 Cardiac pathological changes associated with COVID-19.

JAMA Cardiology | Brief Report

Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases

Diana Lindner, PhD; Antonia Fitzek, MD; Hanna Bräuninger, MS; Ganna Aleshcheva, PhD; Caroline Edler, MD; Kira Meissner; Katharina Scherschel, PhD; Paulus Kirchhof, MD; Felicitas Escher, MD; Heinz-Peter Schultheiss, MD; Stefan Blankenberg, MD; Klaus Püschel, MD; Dirk Westermann, MD

IMPORTANCE Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can be documented in various tissues, but the frequency of cardiac involvement as well as possible consequences are unknown.

OBJECTIVE To evaluate the presence of SARS-CoV-2 in the myocardial tissue from autopsy cases and to document a possible cardiac response to that infection.

DESIGN, SETTING, AND PARTICIPANTS This cohort study used data from consecutive autopsy cases from Germany between April 8 and April 18, 2020. All patients had tested positive for SARS-CoV-2 in pharyngeal swab tests.

EXPOSURES Patients who died of coronavirus disease 2019.

MAIN OUTCOMES AND MEASURES Incidence of SARS-CoV-2 positivity in cardiac tissue as well as $CD3^+$, $CD45^+$, and $CD68^+$ cells in the myocardium and gene expression of tumor necrosis growth factor α, interferon γ, chemokine ligand 5, as well as interleukin-6, -8, and -18.

RESULTS Cardiac tissue from 39 consecutive autopsy cases were included. The median (interquartile range) age of patients was 85 (78-89) years, and 23 (59.0%) were women. SARS-CoV-2 could be documented in 24 of 39 patients (61.5%). Viral load above 1000 copies per µg RNA could be documented in 16 of 39 patients (41.0%). A cytokine response panel consisting of 6 proinflammatory genes was increased in those 16 patients compared with 15 patients without any SARS-CoV-2 in the heart. Comparison of 15 patients without cardiac infection with 16 patients with more than 1000 copies revealed no inflammatory cell infiltrates or differences in leukocyte numbers per high power field.

CONCLUSIONS AND RELEVANCE In this analysis of autopsy cases, viral presence within the myocardium could be documented. While a response to this infection could be reported in cases with higher virus load vs no virus infection, this was not associated with an influx of inflammatory cells. Future investigations should focus on evaluating the long-term consequences of this cardiac involvement.

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Editorial page 1216

Supplemental content

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CORRESPONDENCE

Guillain–Barré Syndrome Associated with SARS-CoV-2

TO THE EDITOR:

From February 28 through March 21, 2020, in three hospitals in northern Italy, we examined five patients who had Guillain–Barré syndrome after the onset of coronavirus disease 2019 (Covid-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). During that period, an estimated 1000 to 1200 patients with Covid-19 were admitted to these hospitals. Four of the patients in this series had a positive nasopharyngeal swab for SARS-CoV-2 at the onset of the neurologic syndrome, and one had a negative nasopharyngeal swab and negative bronchoalveolar lavage but subsequently had a positive serologic test for the virus. Detailed case reports are provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org.

The first symptoms of Guillain–Barré syndrome were lower-limb weakness and paresthesia in four patients and facial diplegia followed by ataxia and paresthesia in one patient (Table 1). Generalized, flaccid tetraparesis or tetraplegia evolved over a period of 36 hours to 4 days in four patients; three received mechanical ventilation. The interval between the onset of symptoms of Covid-19 and the first symptoms of Guillain–Barré syndrome ranged from 5 to 10 days (Table 1 and Fig. S1 in the Supplementary Appendix). None of the patients had dysautonomic features.

Table 1.

Characteristics of Five Patients with Guillain–Barré Syndrome after the Onset of Covid-19.

On analysis of the cerebrospinal fluid (CSF), two patients had a normal protein level and all the patients had a white-cell count of less than 5 per cubic millimeter. Antiganglioside antibodies were absent in the three patients who were tested. In all the patients, a real-time polymerase-chain-reaction assay of the CSF was negative for SARS-CoV-2. Results of electrophysiological studies are shown in Table S1. Compound muscle action potential amplitudes were low but could be obtained; two patients had prolonged motor distal latencies. On electromyography, fibrillation potentials were present in three patients initially; in another patient, they were absent initially but were present at 12 days. The findings were generally consistent with an axonal variant of Guillain–Barré syndrome in three patients and with a demyelinating process in two patients.[1] Magnetic

June 25, 2020
N Engl J Med 2020; 382:2574-2576
DOI: 10.1056/NEJMc2009191
Metrics

Journal of Neurology (2020) 267:2799–2802
https://doi.org/10.1007/s00415-020-09951-9

LETTER TO THE EDITORS

COVID-19-associated acute disseminated encephalomyelitis (ADEM)

Timothy Parsons[1,2] · Sarah Banks[1,2] · Chay Bae[2] · Joel Gelber[1] · Hussein Alahmadi[1] · Matthew Tichauer[1,2]

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Abstract

A 51-year-old woman with COVID-19 infection developed coma and an impaired oculocephalic response to one side. MRI of the brain demonstrated acute multifocal demyelinating lesions, and CSF testing did not identify a direct cerebral infection. High-dose steroids followed by a course of IVIG was administered, and the patient regained consciousness over the course of several weeks. As more patients reach the weeks after initial infection with COVID-19, acute disseminated encephalomyelitis should be considered a potentially treatable cause of profound encephalopathy or multifocal neurological deficits.

Keywords ADEM · Post-infectious · COVID-19 · Coronavirus · Demyelinating disease

OBSERVATION: CASE REPORT

Myasthenia Gravis Associated With SARS-CoV-2 Infection

Background: Some patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have neurologic symptoms (1–3). Some observers propose that these symptoms are caused by viral infection of nerve cells (4), but the possibility exists that these symptoms might be produced by autoimmune mechanisms (1–4). Myasthenia gravis is an autoimmune disease in which antibodies bind to acetylcholine receptors (AChRs) or to functionally related molecules in the postsynaptic membrane at the neuromuscular junction (5).

Objective: To describe 3 patients without previous neurologic or autoimmune disorders who were diagnosed with myasthenia gravis after the onset of coronavirus disease 2019 (COVID-19).

Case Report: Patient 1 was a 64-year-old man who had fever as high as 39 °C for 4 days. Five days after fever onset, he developed diplopia and muscular fatigability. Although his chest radiograph was normal, nasopharyngeal swab and real-time reverse transcriptase polymerase chain reaction (RT-PCR) testing for COVID-19 showed a positive result. We suspected myasthenia gravis because of his symptoms. His neurologic examination was unremarkable. Computed tomography (CT) of the thorax excluded thymoma. Repetitive stimulation of the facial nerve showed a 57% decrement, confirming involvement of the postsynaptic neuromuscular junction, and the concentration of AChR antibodies in his serum was elevated (22.8 pmol/L; normal value, <0.4 pmol/L). We administered pyridostigmine bromide and prednisone, and the patient had a response typical for someone with myasthenia gravis.

Patient 2 was a 68-year-old man who had fever as high as 38.8 °C for 7 days. On day 7, he developed general muscular fatigability, diplopia, and dysphagia. Although his chest CT scan was normal, nasopharyngeal swab and RT-PCR testing for COVID-19 yielded positive results. We suspected myasthenia gravis because of his symptoms. His neurologic examination was normal, and his chest CT scan excluded thymoma. Repetitive nerve stimulation showed a postsynaptic deficit of neuromuscular transmission of the facial (52%) and ulnar (21%) nerves. His serum AChR antibody level was elevated (27.6 pmol/L). He improved after 1 cycle of intravenous immunoglobulin treatment.

Patient 3 was a 71-year-old woman who had a cough and fever to 38.6 °C for 6 days. Nasopharyngeal swab and RT-PCR testing for COVID-19 showed a negative result. Five days after her symptoms began, she developed bilateral ocular ptosis, diplopia, and hypophonia. Thorax CT revealed bilateral interstitial pneumonia and excluded thymoma. One day later, she developed dysphagia and respiratory failure and was transferred to the intensive care unit, where she received mechanical ventilation through a tracheostomy. Repetitive nerve stimulation showed a postsynaptic deficit of neuromuscular transmission of the ulnar nerve (56%), and her serum AChR antibody level was elevated (35.6 pmol/L). Five days later, she had a second nasopharyngeal swab test for COVID-19, and the result was positive. Plasmapheresis was started; she improved and was extubated. This patient received hydroxychloroquine the day after the onset of her first neurologic symptoms (withdrawn a day later), so we do not believe that it caused her symptoms of myasthenia gravis.

Additional information about these patients is provided in the **Table**.

Discussion: We describe what we believe are the first 3 reported cases of AChR antibody–positive myasthenia gravis after COVID-19. These observations are consistent with reports of other infections that induce autoimmune disorders, as well as with the growing evidence of other neurologic disorders with presumed autoimmune mechanisms after COVID-19 onset (1–3). We note that symptoms of myasthenia gravis appeared within 5 to 7 days after fever onset in all 3 patients, and the time from presumed infection with SARS-CoV-2 to the beginning of myasthenia gravis symptoms is consistent with the time from infection to symptoms in other neurologic disorders triggered by infections (2, 3). Several possible explanations exist. For example, antibodies that are directed against SARS-CoV-2 proteins may cross-react with AChR subunits, because the virus has epitopes that are similar to components of the neuromuscular junction; this is known to occur in other neurologic autoimmune disorders after infection. Alternatively, COVID-19 infection may break immunologic self-tolerance.

Table. Clinical and Demographic Data of 3 Patients With Myasthenia Gravis Associated With COVID-19 Infection

Patient	Age, *y*	Sex	Previous Neurologic or Autoimmune Diseases	Body Temperature at Hospitalization, °C	Myasthenia Gravis Symptom Onset	Pulmonary Manifestations on CT scan	Therapy
1	64	M	No	36.5	5 d after fever	None	Pyridostigmine bromide: 60 mg 4× daily Prednisone: 75 mg/d
2	68	M	No	36	7 d after fever	None	IVI: 0.4 g/kg/d for 5 d
3	71	F	No	37.6	5 d after fever	Bilateral interstitial pneumonia	Plasmapheresis: 3 sessions the 1st wk, 2 sessions the 2nd wk, 1 session the 3rd wk; dosage: 1 volume plasma/1 volume saline + 2 L albumin Lopinavir/ritonavir: 400/100 mg 2× daily Hydroxychloroquine: 200 mg 2× daily

COVID = coronavirus disease 2019; CT = computed tomography; F = female; IVI = intravenous immunoglobulin; M = male.

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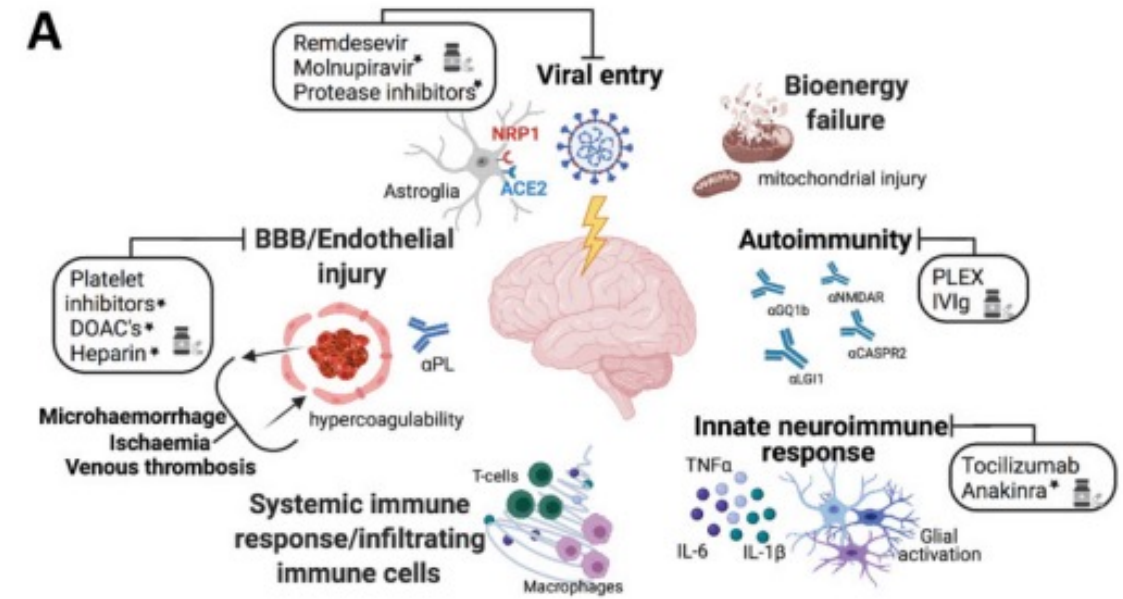
https://doi.org/10.1093/brain/awab302 BRAIN 2021: 144; 3576–3588 | 3576

BRAIN
REVIEW ARTICLE

Acute and chronic neurological disorders in COVID-19: potential mechanisms of disease

Erin F. Balcom,[1] Avindra Nath[2] and Christopher Power[1]

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by SARS-CoV-2 infection and is associated with both acute and chronic disorders affecting the nervous system. Acute neurological disorders affecting patients with COVID-19 range widely from anosmia, stroke, encephalopathy/encephalitis, and seizures to Guillain–Barré syndrome. Chronic neurological sequelae are less well defined although exercise intolerance, dysautonomia, pain, as well as neurocognitive and psychiatric dysfunctions are commonly reported. Molecular analyses of CSF and neuropathological studies highlight both vascular and immunologic perturbations. Low levels of viral RNA have been detected in the brains of few acutely ill individuals. Potential pathogenic mechanisms in the acute phase include coagulopathies with associated cerebral hypoxic-ischaemic injury, blood–brain barrier abnormalities with endotheliopathy and possibly viral neuroinvasion accompanied by neuro-immune responses. Established diagnostic tools are limited by a lack of clearly defined COVID-19 specific neurological syndromes. Future interventions will require delineation of specific neurological syndromes, diagnostic algorithm development and uncovering the underlying disease mechanisms that will guide effective therapies.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BBB/Endothelial injury
Platelet inhibitors*
DOAC's*
Heparin*
αPL
hypercoagulability
Microhaemorrhage
Ischaemia
Venous thrombosis
Autoimmunity
αGQ1b
αNMDAR
αCASPR2
αLGI1
PLEX
IVIg
Innate neuroimmune response
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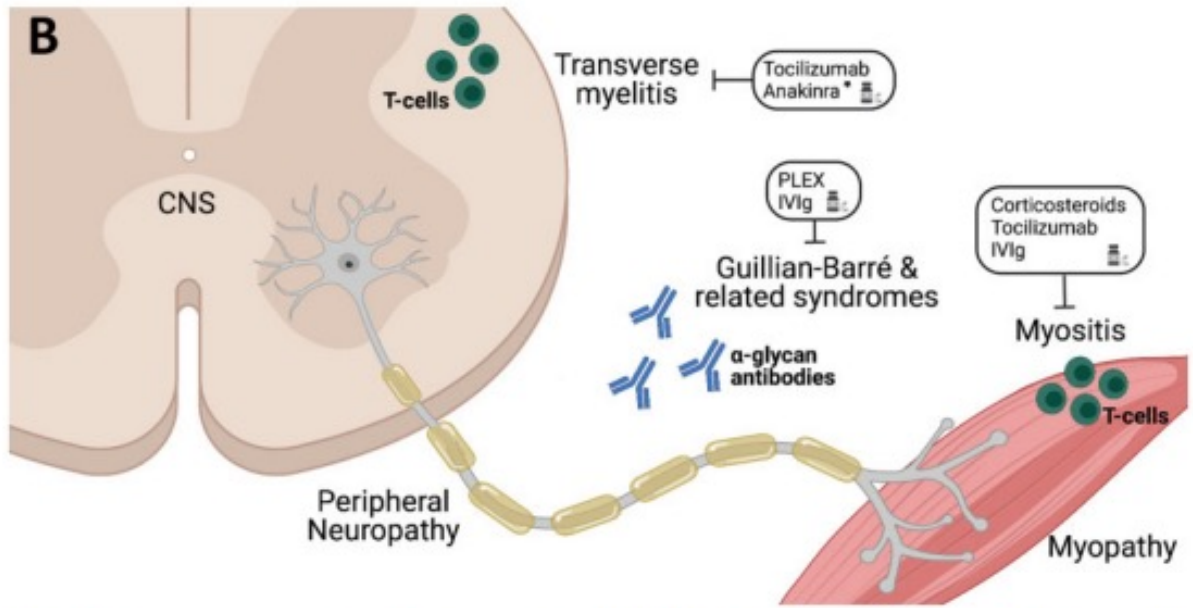
T-cells
Macrophages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Transverse myelitis
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CNS
PLEX
IVIg
Guillian-Barré & related syndromes
α-glycan antibodies
Corticosteroids
Tocilizumab
IVIg
Myositis
T-cells
Peripheral Neuropathy
Myopathy

Table 1 Proposed neuropathogenic mechanisms in SARS-CoV-2 infection

Acute neurological syndromes	Proposed mechanisms	References	Proposed therapies
Anosmia/ageusia	Direct infection of olfactory bulb Inflammation of olfactory tract	Meinhardt *et al.*,[14] Lu *et al.*[15]	None
Stroke	Hypercoagulability/endothelial damage	Hernández-Fernández *et al.*,[16] Goshua *et al.*,[17] Yaghi *et al.*[18]	Prophylactic anticoagulation is currently under investigation; no clear guidelines to date Successful treatment with thrombolysis and mechanical thrombectomy reported
Encephalitis	Viral neuro-invasion Disrupted blood–brain barrier Autoimmunity	Nampoothiri *et al.*,[19] Meinhardt *et al.*[14] Alexopoulos *et al.*[20] Cao *et al.*,[21] Guilmot *et al.*,[22] Pilotto *et al.*[23,24]	Favourable responses to systemic corticosteroids, tocilizumab, and PLEX are observed in a subset of cases
Encephalopathy	Metabolic dysfunction Hypoxia/ischaemia Cerebral microthrombi Cytokine storm (systemic)	Bryce *et al.*,[25] Antony and Haneef,[26] Lee *et al.*,[27] Lin *et al.*[28]	Generally supportive, reported success with tocilizumab in case reports
Peripheral neuropathy	Critical illness neuropathy Molecular mimicry (GBS and variants)	Cabañes-Martínez *et al.*[29] Dalakas,[30] Temme *et al.*[31]	Supportive Standard therapy: IVIg, PLEX
Myositis	Bioenergetic dysfunction Immune-mediated myositis	Beydon *et al.*,[32] Dalakas,[30] Zhang *et al.*[33]	Favourable responses to steroids, IVIg and tocilizumab reported
Chronic neurological sequelae			
Fatigue	Chronic neuroinflammation Neuroendocrine dysfunction Persistent respiratory and cardiac damage	Pandharipande *et al.*,[34] Raman *et al.*,[35] Mongioì *et al.*[36]	None
Cognitive impairment	Chronic neuroinflammation Frontoparietal hypometabolism	Blazhenets *et al.*,[37] Guedj *et al.*[38]	None, demonstrated to improve over months
Depression/altered mood	Stress (isolation, post-traumatic stress)	Rogers *et al.*[39]	No specific therapies proposed or tested for post-COVID-19 patients

PLEX = plasma exchange.

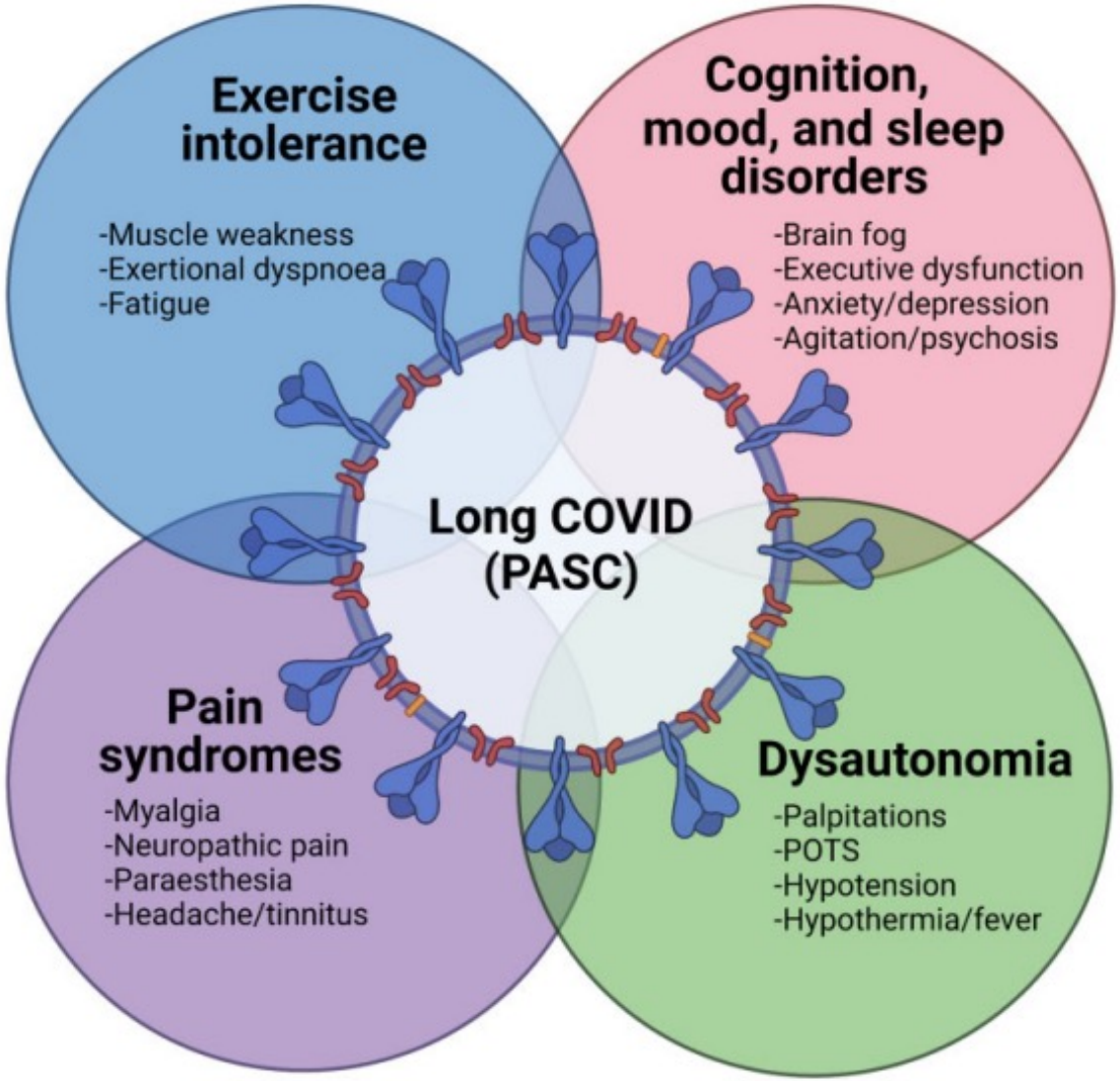

Figure 3 Chronic neurological sequelae of COVID-19. Several long-term neurological syndromes result from SARS-CoV-2 among hospital- and community-treated patients, termed long COVID or post-acute sequelae of COVID-19 (PASC). These syndromes include neurocognitive, mood and sleep disorders, dysautonomia, diverse pain syndromes, as well as marked exercise intolerance and fatigue. These protracted syndromes remain to be fully defined in longitudinal cohort studies.

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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

SARS-CoV-2 and neurodegenerative diseases: what we know and what we don't

Paul Lingor[1,2,3] · Antonia F. Demleitner[1] · Andreas W. Wolff[1] · Emily Feneberg[1]

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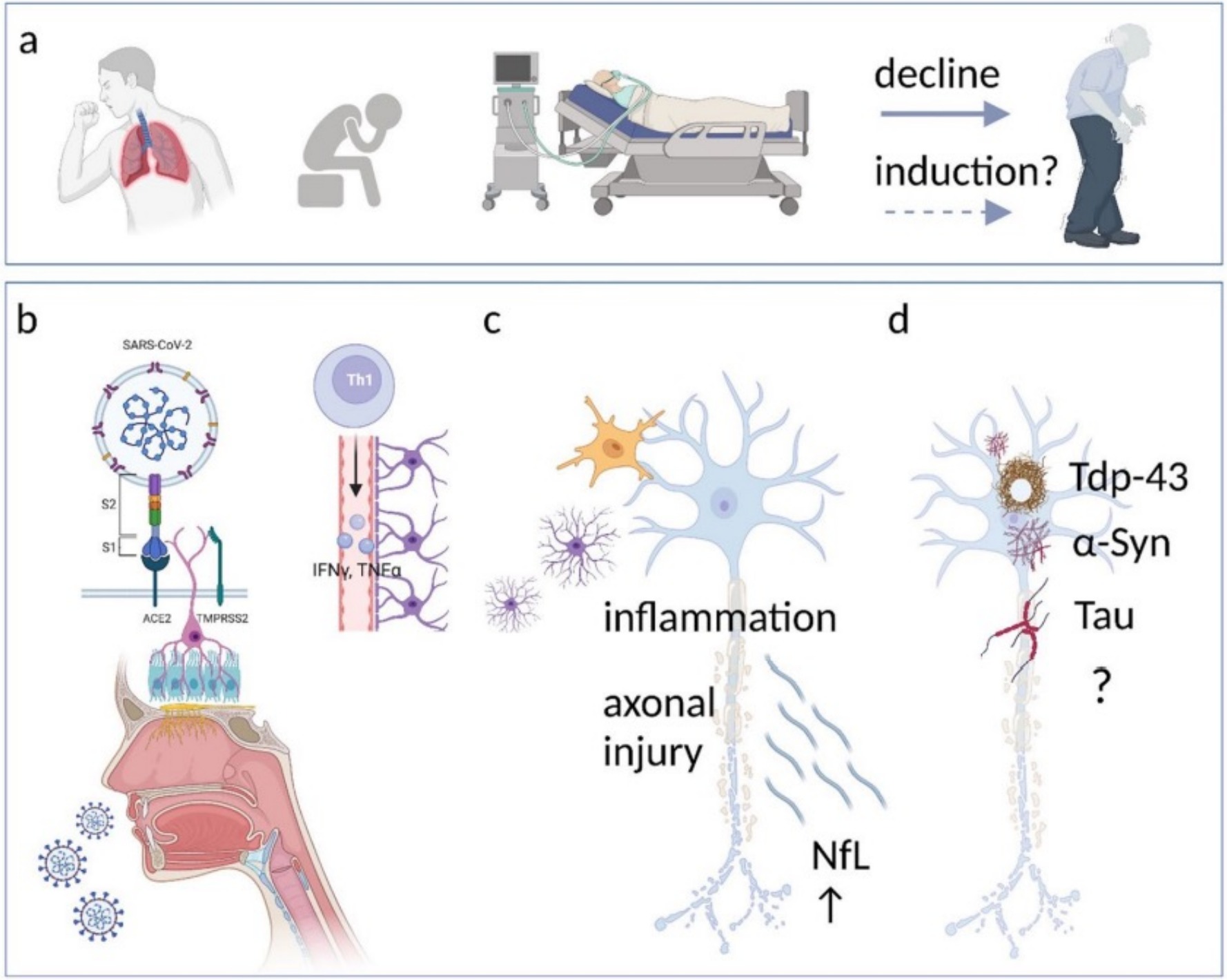
Abstract

Infection of the CNS with the SARS-CoV-2 can occur via different routes and results in para- or post-infectious manifestations with a variety of neurological symptoms. In patients with neurodegenerative diseases, SARS-CoV-2 is often associated with a higher fatality rate, which is a relevant problem in increasingly older populations. Apart from the direct consequences of an infection in patients with neurodegenerative diseases, indirect consequences of the pandemic such as limited access to care facilities and treatment have negative effects on the course of these chronic disorders. The occurrence of long-lasting neurological symptoms after infection with SARS-CoV-2 indicates a prolonged impact on the CNS. However, while it is known that SARS-CoV-2 affects neuronal populations that are relevant in the pathogenesis of neurodegenerative diseases, it is yet unclear whether an infection with SARS-CoV-2 is sufficient to trigger neurodegeneration. Reflecting on the impact of SARS-CoV-2 on neurodegeneration, we provide a concise overview on the current knowledge of SARS-CoV-2-induced pathology in the CNS and discuss yet open questions in the field.

Keywords COVID-19 · Neurodegeneration · Parkinson's disease · Neurological symptoms · Alzheimer's disease · SARS-CoV-2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Article

SARS-CoV-2 is associated with changes in brain structure in UK Biobank

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Check for updates

Gwenaëlle Douaud[1,2], Soojin Lee[1], Fidel Alfaro-Almagro[1], Christoph Arthofer[1], Chaoyue Wang[1], Paul McCarthy[1], Frederik Lange[1], Jesper L. R. Andersson[1], Ludovica Griffanti[1,2], Eugene Duff[1,3], Saad Jbabdi[1], Bernd Taschler[1], Peter Keating[4], Anderson M. Winkler[5], Rory Collins[6], Paul M. Matthews[7], Naomi Allen[6], Karla L. Miller[1], Thomas E. Nichols[8] & Stephen M. Smith[1]

There is strong evidence of brain-related abnormalities in COVID-19[1–13]. However, it remains unknown whether the impact of SARS-CoV-2 infection can be detected in milder cases, and whether this can reveal possible mechanisms contributing to brain pathology. Here we investigated brain changes in 785 participants of UK Biobank (aged 51–81 years) who were imaged twice using magnetic resonance imaging, including 401 cases who tested positive for infection with SARS-CoV-2 between their two scans—with 141 days on average separating their diagnosis and the second scan—as well as 384 controls. The availability of pre-infection imaging data reduces the likelihood of pre-existing risk factors being misinterpreted as disease effects. We identified significant longitudinal effects when comparing the two groups, including (1) a greater reduction in grey matter thickness and tissue contrast in the orbitofrontal cortex and parahippocampal gyrus; (2) greater changes in markers of tissue damage in regions that are functionally connected to the primary olfactory cortex; and (3) a greater reduction in global brain size in the SARS-CoV-2 cases. The participants who were infected with SARS-CoV-2 also showed on average a greater cognitive decline between the two time points. Importantly, these imaging and cognitive longitudinal effects were still observed after excluding the 15 patients who had been hospitalised. These mainly limbic brain imaging results may be the in vivo hallmarks of a degenerative spread of the disease through olfactory pathways, of neuroinflammatory events, or of the loss of sensory input due to anosmia. Whether this deleterious effect can be partially reversed, or whether these effects will persist in the long term, remains to be investigated with additional follow-up.

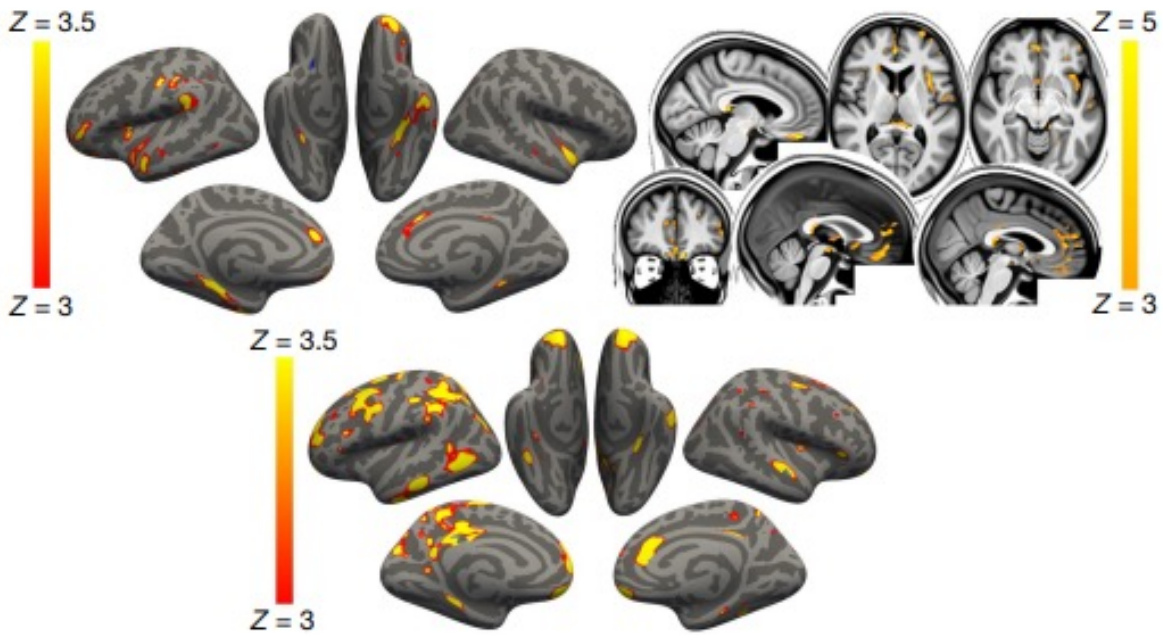

Fig. 2 | Vertex-wise and voxel-wise longitudinal group differences in grey matter thickness and mean diffusivity changes. Top, the main analysis (Model 1): the thresholded map ($|Z| > 3$) shows that the strongest, localised reductions in grey matter thickness in the 401 infected participants compared with the 384 controls are bilaterally in the parahippocampal gyrus, anterior cingulate cortex and temporal pole, as well as in the left orbitofrontal cortex, insula and supramarginal gyrus. Similarly, the strongest longitudinal differences in mean diffusivity ($|Z| > 3$, left is shown on the right) could be seen

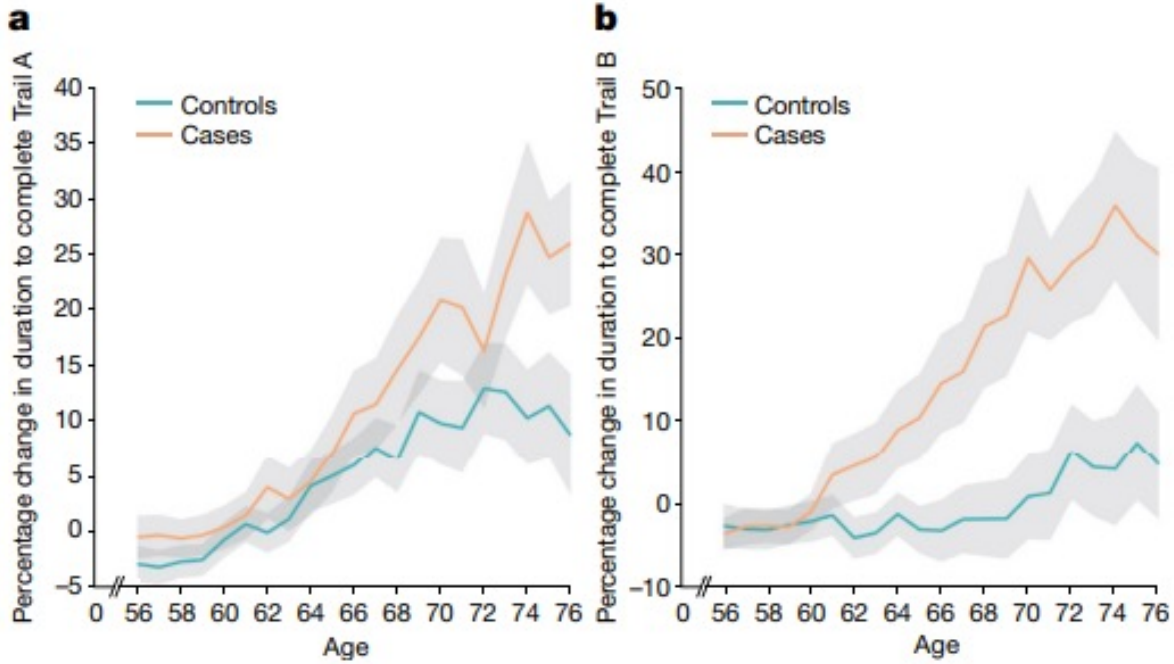

Fig. 3 | Significant longitudinal differences in cognition. a, **b**, The percentage longitudinal change for SARS-CoV-2-positive cases and controls in the duration to complete trails A (**a**) and B (**b**) of the UK Biobank Trail Making Test. The absolute baseline (used to convert longitudinal change into percentage change) was estimated across the 785 participants. These curves were created using a ten-year sliding window across cases and controls (s.e. values are shown in grey).

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REVIEW

Brain Pathology

SARS-CoV-2 and the brain: A review of the current knowledge on neuropathology in COVID-19

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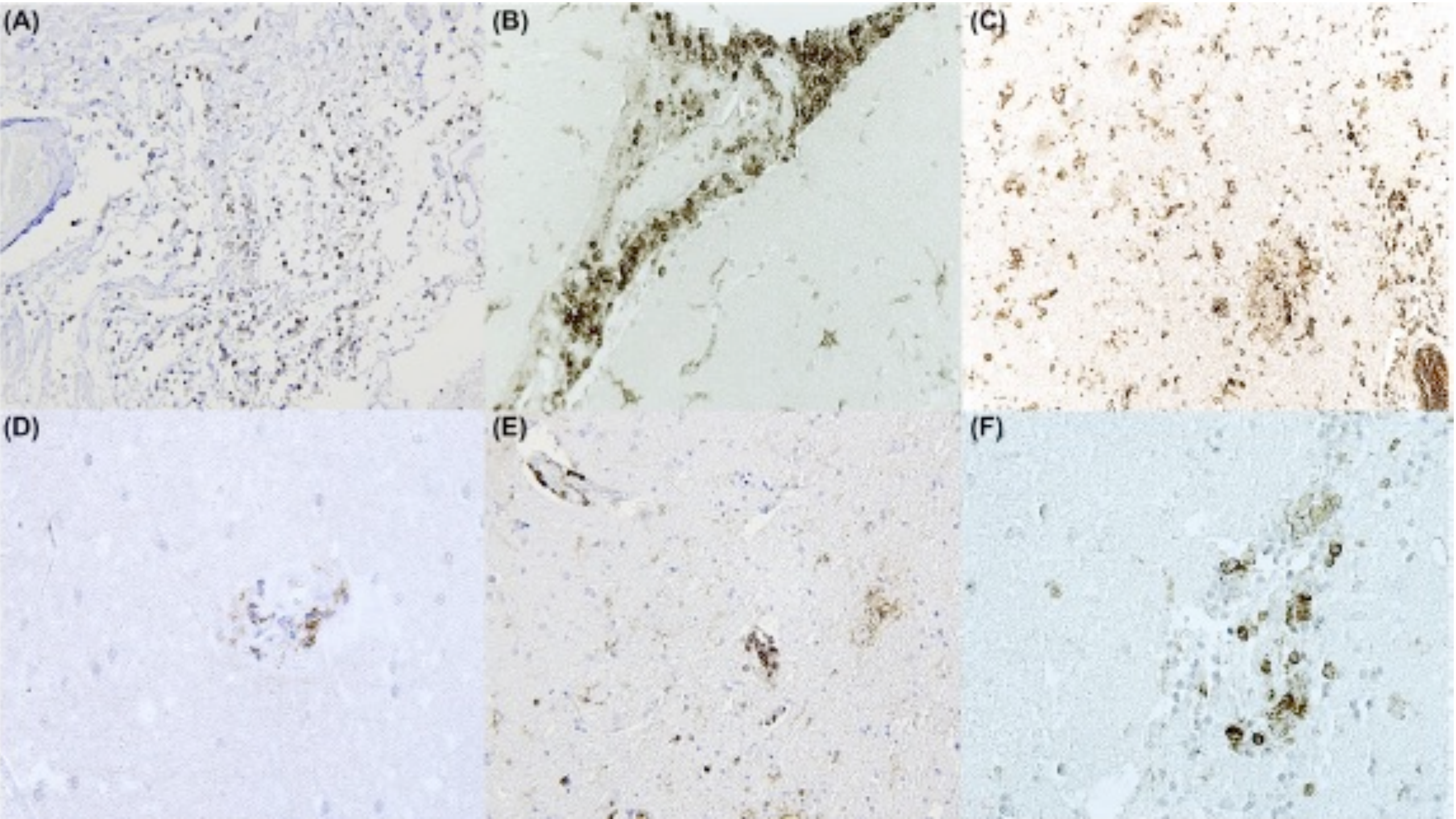
Abstract

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), the new coronavirus responsible for the pandemic disease in the last year, is able to affect the central nervous system (CNS). Compared with its well-known pulmonary tropism and respiratory complications, little has been studied about SARS-CoV-2 neurotropism and pathogenesis of its neurological manifestations, but also about postmortem histopathological findings in the CNS of patients who died from COVID-19 (coronavirus disease 2019). We present a systematic review, carried out according to the Preferred Reporting Items for Systematic Review standards, of the neuropathological features of COVID-19. We found 21 scientific papers, the majority of which refer to postmortem examinations; the total amount of cases is 197. Hypoxic changes are the most frequently reported alteration of brain tissue, followed by ischemic and hemorrhagic lesions and reactive astrogliosis and microgliosis. These findings do not seem to be specific to SARS-CoV-2 infection, they are more likely because of systemic inflammation and coagulopathy caused by COVID-19. More studies are needed to confirm this hypothesis and to detect other possible alterations of neural tissue. Brain examination of patients dead from COVID-19 should be included in a protocol of standardized criteria to perform autopsies on these subjects.

KEYWORDS
autopsy, central nervous system, COVID-19, histology, neurological manifestation, neuropathology

Main brain findings	Number of cases	References
Hypoxic changes (including red neurons)	58 (29.4%)	(20, 37, 38, 43, 45, 46, 48, 50, 52, 53, 56)
Microthrombi	21 (10.6%)	(38, 40, 44, 52, 55)
Ischemic lesions	30 (15.2%)	(37, 38, 44, 50–54)
Micro- and perivascular hemorrhages	24 (12.2%)	(20, 38, 42, 44, 48, 50, 52, 53)
Hemorrhagic lesions	13 (6.6%)	(37, 38, 51, 53, 55)
Microgliosis and microglia activation (with or without nodules)	74 (37.6%)	(20, 37, 43, 46, 47, 49, 50, 52–54)
Astrogliosis	52 (26.4%)	(43, 49)
Parenchymal or perivascular inflammatory infiltrates	31 (15.7%)	(38, 40, 46–48, 50, 52–54, 56)
Leptomeningeal inflammation	11 (5.6%)	(44–46, 50, 52)
Olfactory bulb involvement (cell injury or virus RNA detection)	57 (28.9%)	(40, 43, 46, 49, 50, 52)


(A)
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(F)

of colon carcinoma cell lines (CACo) and gut organoids [93]. The true risk and relevance of SARS-CoV-2 transmission via a fecal-oral route remains unclear and seems to be of rather limited importance. Immunohistochemistry and single-cell transcriptome data revealed expression of ACE2 and TMPRSS2 in enterocytes of the small intestine and colon, most abundant in the ileum [60, 169]. Data of endoscopic samples or surgical specimens is sparse and so far, consists only of small case series or case reports. In COVID-19 patients with gastrointestinal symptoms, structural damage has been variable and ranges from limited and focal inflammation with interstitial edema accompanied by plasmacellular and lymphocytic infiltrates, up to substantial ulceration and necrosis of the mucosa. Notably, different studies confirmed viral RNA and antigens in intestinal epithelial cells as well as in macrophages and lymphocytes suggesting active SARS-CoV-2 replication in the intestine.

Nervous system and skeletal muscle

SARS-CoV-2 invasion in the central nervous system (CNS) occurs via the blood or nerves. A hematogenous route is supported by the fact that COVID-19 leads to viremia and SARS-CoV-2 targets brain endothelial cells [106, 108, 139]. Also, SARS-CoV-2 is not only transported through brain endothelial cells but also replicates in these [90]. The olfactory route and transport along vagal nerves have been suggested as a CNS entry port. Dysfunction of the olfactory system is a key symptom of COVID-19 and SARS-CoV-2 colonizes the nasal cavity. If SARS-CoV-2 additionally transits to CNS via olfactory and sensory nerve endings in the olfactory mucosa is debated with data in favor and opposing this concept [80, 108]. In COVID-19, there is vagal nerve dysfunction and SARS-CoV-2 viral proteins can be found in COVID-19 patients, thus a vagal route of SARS-CoV-2 CNS entry has to be considered [25, 52].

When considering the larger neuropathological studies [34, 106, 108, 132, 139], focal cerebral infarctions are seen in approximately 13% of autopsies. However, cerebral hypoxia in COVID-19 is not consistently defined so far. Global hypoxic-ischemic states, possibly resulting from respiratory

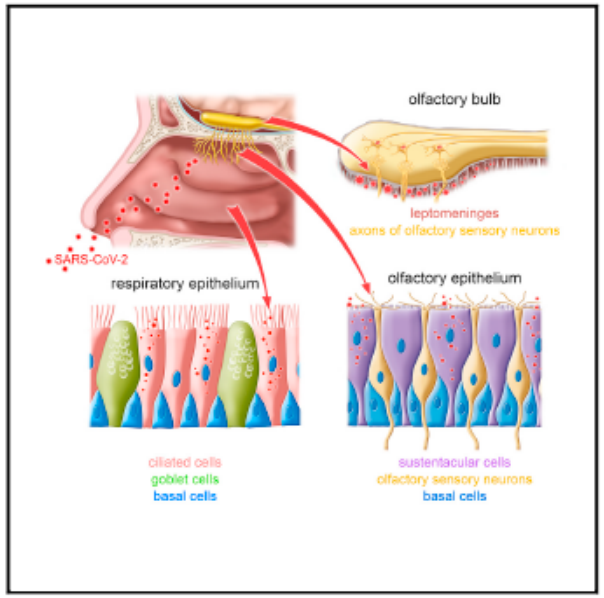
preferentially affected in COVID-19 [165]. Since patients with COVID-19 frequently succumb to bacterial superinfection, sepsis, ventilation, and polypharmacotherapy as well as long-term intensive care unit (ICU) stays with an isolating environment/deafferentation, comparative studies with similar clinical pictures will be required to identify COVID-19 specific encephalopathic changes. Up to now, there is no evidence of a CNS reservoir for viable SARS-CoV-2 virus [90], even though viral RNA or protein may be found at the CNS barriers. A future challenge is the identification of how the CNS contributes to symptoms of the post-COVID syndrome, such as fatigue, headaches, anosmia, muscle weakness, and cognitive dysfunction; it is still very early days. Although there are already large studies on post-COVID, with thousands of study participants [143], the time span is not sufficient to be able to say how long-term consequences will develop. The patients presenting with neurological signs of post-COVID are probably a heterogenous group with some having a dysregulated microbiome, others alteration of the vascular system or dysfunctional brainstem signaling, as well as others with ongoing low-level inflammation or autoimmunity triggered in susceptible hosts [128].

COVID-19 can affect the peripheral neural system meeting diagnostic criteria for acute polyradiculoneuropathy. Early in the course of the pandemic, it was suggested that similar to other viruses, SARS-CoV-2 might directly infect peripheral neurons or trigger Guillain-Barré syndrome (GBS) [55, 141]. However, later epidemiological studies found no link of GBS and SARS-CoV-2 [79]. Similarly, direct infection of skeletal muscle fibers or autoimmune myopathy/myositis triggered by SARS-CoV-2 have been suggested to cause myalgia, muscle weakness, and elevated creatine kinase (CK) levels that are frequently observed in COVID-19 patients [55] and were more pronounced in critically ill patients, compared to mildly affected individuals [103]. A post-mortem case control study could not detect signs of infection of skeletal muscle, but identified myositis with different levels of severity in COVID-19. Inflammation of the muscle was correlating with disease duration, supporting a postinfectious, immune-mediated pathology [12].

Cell

Visualizing in deceased COVID-19 patients how SARS-CoV-2 attacks the respiratory and olfactory mucosae but spares the olfactory bulb

Graphical abstract



Highlights

- A postmortem bedside surgical procedure was developed for COVID-19 and control patients
- Ciliated cells are the main target cell type for SARS-CoV-2 in the respiratory mucosa
- Sustentacular cells (non-neuronal) are the main target cell type in the olfactory mucosa
- No evidence for infection of olfactory sensory neurons or olfactory bulb parenchyma

Authors

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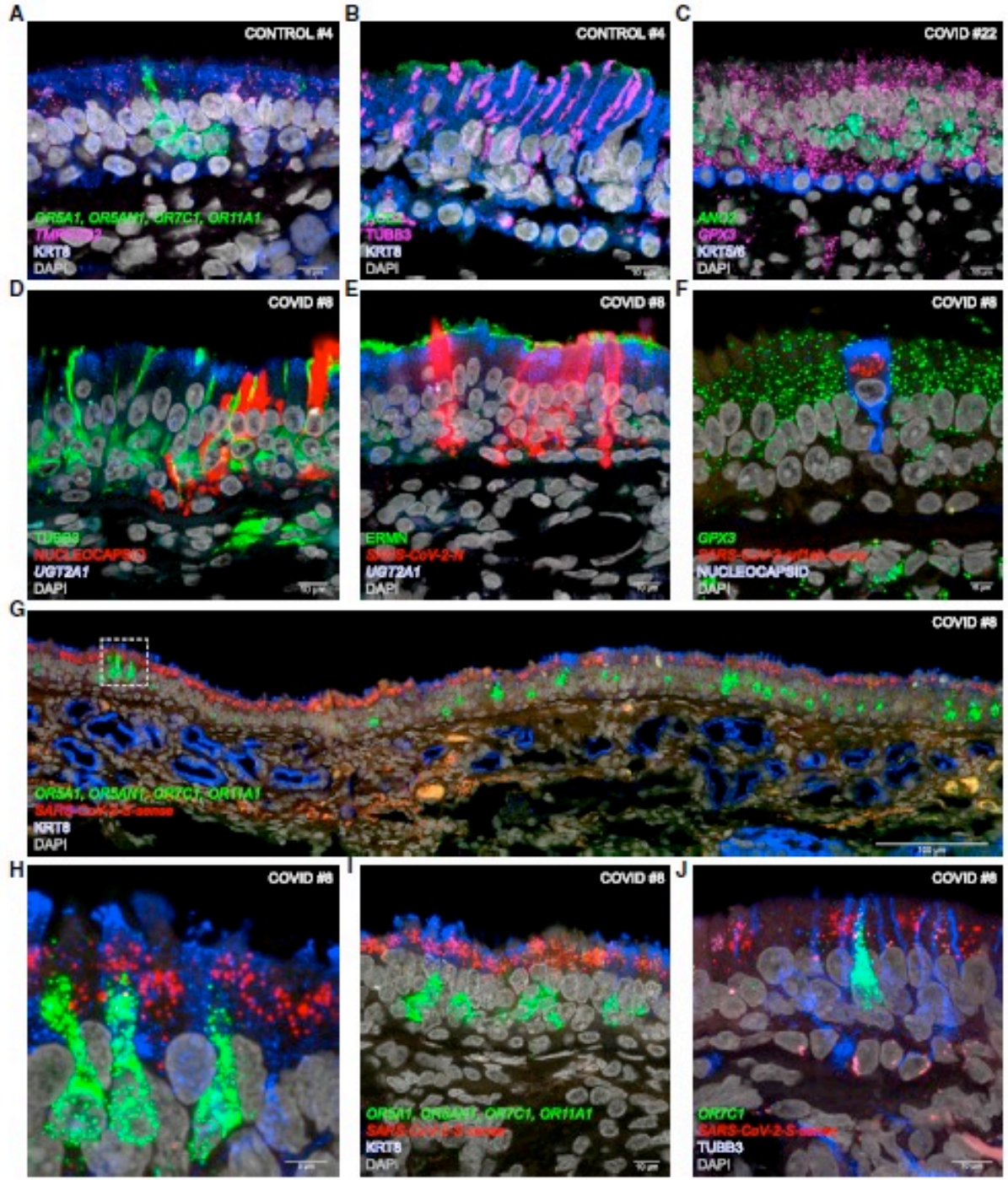
In brief

Postmortem samples of respiratory and olfactory mucosa and whole olfactory bulbs are harvested immediately after the death of COVID-19 patients revealing ciliated cells and sustentacular cells but not olfactory sensory neurons as the main target cell types for SARS-CoV-2 infection and replication.

Khan et al., 2021, Cell *184*, 5932–5949
November 24, 2021
https://doi.org/10.1016/j.cell.2021.10.027

CellPress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KRT8
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C
COVID #22
ANO1
GPX3
KRT5/6
DAPI
D
COVID #8
TUBB3
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