

## Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

**eTable 1. Demographics, medical history and significant autopsy findings**

| Case No. | Age/<br>Sex | Interval btwn<br>Symptom<br>Onset &<br>Death (Day) | Postmortem<br>Swab PCR | COVID-<br>19<br>Infection<br>Severity | Cause of Death  | Comorbidities   | Significant Brain<br>Pathology   | Note |
|----------|-------------|--|------------------------|---------------------------------------|---|---|--|------|
| 1        | 30s/F       | 4  | Pos                    | Mild                                  | Ruptured basilar artery aneurysm                        | HTN   | Ruptured aneurysm, SAH, HIE  |      |
| 2        | 60s/M       | 28   | Pos                    | Critical                              | COVID-19 complications                                  | HTN, hyperlipidemia, CAD, PAD                         | None   |      |
| 3        | 50s/M       | 14   | Pos                    | Critical                              | COVID-19 pneumonia and superimposed bacterial pneumonia | HTN   | None   |      |
| 4        | 60s/M       | 45   | Neg                    | Severe                                | COVID-19 pneumonia                                      | DM, HTN, hyperlipidemia, CAD                          | None   |      |
| 5        | 50s/M       | 21   | ND                     | Severe                                | COVID-19 complications                                  | HTN   | Extensive white matter hemorrhage, intravascular thrombi                                   |      |
| 6        | 20s/M       | 10   | Pos                    | Mild                                  | COVID-19 pneumonia                                      | Transverse myelitis, PE, CAD                          | None   |      |
| 7        | 60s/F       | 18   | Pos                    | Severe                                | PE  | DM, HTN, CAD  | None   |      |
| 8        | 40s/M       | 18   | Pos                    | Moderate                              | COVID-19 complications                                  | AA s/p chemoradiation, meningioma s/p resection       | Radiation necrosis, residual meningioma  |      |
| 9        | 70s/M       | 52   | NA                     | Severe                                | Cardiac arrhythmia                                      | IPF s/p left lung transplant, DM, HTN, hyperlipidemia | Diffuse Lewy body disease  |      |
| 10       | 80s/F       | 110  | NA                     | Mild                                  | Intracerebral hemorrhage                                | DM, HTN, hyperlipidemia, left MCA infarct             | Acute basal ganglia hemorrhage, remote MCA infarct, intermediate AD neuropathologic change |      |
| 11       | 60s/F       | 9  | Pos                    | Critical                              | COVID pneumonia   | CAD   | None   |      |
| 12       | 40s/M       | 10   | Pos                    | Moderate                              | COVID-19 complications                                  | DM, chronic heart failure, CKD                        | None   |      |
| 13       | 60s/M       | 22   | Pos                    | Critical                              | COVID-19 pneumonia and superimposed bronchopneumonia    | DM, HTN, CAD, PAD, hyperlipidemia                     | Global HIE   |      |

**eTable 1. Demographics, medical history and significant autopsy findings (continued)**

| Case No. | Age/<br>Sex | Interval btwn<br>Symptom<br>Onset &<br>Death (Day) | Postmortem<br>Swab PCR | COVID-<br>19<br>Infection<br>Severity | Cause of Death  | Comorbidities                         | Significant Brain<br>Pathology     | Note  |
|----------|-------------|--|------------------------|---------------------------------------|---|---------------------------------------|------------------------------------|---|
| 14       | 40s/F       | 6  | Pos                    | Critical                              | COVID-19 pneumonia                                      | Obesity, DM, HCM, DCM                 | None                               |   |
| 15       | 60s/M       | 35   | NA                     | Critical                              | COVID-19 complications                                  | Obesity, Afib, hyperlipidemia, stroke | None                               |   |
| 16       | 90s/M       | 17   | Pos                    | Severe                                | COVID-19 pneumonia and superimposed bacterial pneumonia | CHF                                   | None                               |   |
| 17       | 60s/M       | 72   | ND                     | Severe                                | COVID-19 complications                                  | DM, HTN, CAD, CHF, COPD               | None                               |   |
| 18       | 80s/F       | 8  | Pos                    | Mild                                  | Ruptured ascending aortic aneurysm                      | HTN, hyperlipidemia                   | None                               |   |
| 19       | 60s/M       | 27   | Neg                    | Critical                              | COVID-19 pneumonia                                      | Obesity, DM, HTN                      | None                               |   |
| 20       | 50s/F       | 37   | Pos                    | Critical                              | Complications of COPD                                   | COPD, CHF, DVT                        | None                               |   |
| 21       | 70s/F       | 27   | Pos                    | Severe                                | COVID-19 pneumonia and superimposed bacterial pneumonia | HTN, hyperlipidemia                   | None                               |   |
| 22       | 30s/F       | Unknown  | Pos                    | Unknown                               | COVID-19 pneumonia                                      | Obesity                               | None                               |   |
| 23       | 30s/M       | -  | Pos                    | No symptoms                           | Acute aspiration  | Autism                                | None                               |   |
| 1C       | 50s/F       | -  | NA                     | -                                     | Diffuse peritoneal carcinomatosis                       | HTN                                   | HIE                                |   |
| 2C       | 60s/M       | -  | NA                     | -                                     | Bacterial bronchopneumonia                              | HTN, CAD, Afib, PAD, FTD              | FTLD-TDP                           | Hospitalization: 7D   |
| 3C       | 50s/F       | -  | NA                     | -                                     | Bacterial pneumonia                                     | IPF s/p bilateral lung transplant     | None                               | ARDS; Mechanical ventilation +; Hospitalization: 37D (ICU: 12D) |
| 4C       | 70s/M       | -  | NA                     | -                                     | Ruptured AAA  | Stroke                                | Remote frontal infarct, global HIE |   |
| 5C       | 20s/F       | -  | NA                     | -                                     | Diabetic ketoacidosis                                   | DM                                    | None                               | Aspiration pneumonitis  |
| 6C       | 30s/M       | -  | NA                     | -                                     | EBV-induced HLH   |                                       | HIE, hepatic encephalopathy        | ICU: 2D   |

**eTable 1. Demographics, medical history and significant autopsy findings (continued)**

| Case No. | Age/<br>Sex | Interval btwn<br>Symptom<br>Onset &<br>Death (Day) | Postmortem<br>Swab PCR | COVID-<br>19<br>Infection<br>Severity | Cause of Death               | Comorbidities  | Significant Brain<br>Pathology   | Note  |
|----------|-------------|--|------------------------|---------------------------------------|------------------------------|--|--|---|
| 7C       | 20s/M       | -  | NA                     | -                                     | VSD due to chest trauma      |  | None   | Mechanical ventilation +; ECMO +; ICU: 36D                                    |
| 8C       | 60s/M       | -  | NA                     | -                                     | Hepatic artery thrombosis    | DM, HTN, CAD, NASH and HCC s/p recent liver transplant | Hepatic encephalopathy   | ICU: 5D   |
| 9C       | 40s/F       | -  | NA                     | -                                     | Bacterial endocarditis       | ESRD, HFpEF, nephrotic syndrome                        | None   | Pneumonia with ARDS; Mechanical ventilation +; Hospitalization: 18D (ICU: 7D) |
| 10C      | 20s/F       | -  | Neg                    | -                                     | Non-COVID-19 viral pneumonia |  | None   |   |
| 11C      | 40s/M       | -  | NA                     | -                                     | Ruptured AVM                 |  | Cerebellar hemorrhage, AVM s/p craniotomy, SAH, HIE  | Mechanical ventilation +; ICU: 20D  |
| 12C      | 50s/M       | -  | NA                     | -                                     | Myocardial infarction        | DM, HTN, CKD   | Multifocal frontoparietal hemorrhagic infarcts, SAH, HIE, intermediate AD neuropathologic change | Mechanical ventilation +; ICU: 8D   |
| 13C      | 60s/F       | -  | NA                     | -                                     | Septic shock                 | DM, HTN  | Meningitis   |   |
| 14C      | 70s/F       | -  | NA                     | -                                     | Candida urosepsis            | DM, breast cancer                                      | None   | Hospitalization: 16D  |

Abbreviations: AA: anaplastic astrocytoma; AAA: abdominal aortic aneurysm; AD: Alzheimer disease; Afib: atrial fibrillation; ARDS: acute respiratory distress syndrome; AVM: arteriovenous malformation; CAD: coronary artery disease; CHF: congestive heart failure; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; DCM: dilated cardiomyopathy; DM: diabetes mellitus; DVT: deep vein thrombosis; EBV: Epstein-Barr virus; ECMO: extracorporeal membranous oxygenation; FTD: frontotemporal dementia; FTLD-TDP: frontotemporal lobar degeneration with TDP-43 inclusions; HCC: hepatocellular carcinoma; HCM: hypertrophic cardiomyopathy; HFpEF: heart failure with preserved ejection fraction; HIE: hypoxic-ischemic encephalopathy; HLH: hemophagocytic lymphohistiocytosis; HTN: hypertension; ICU: intensive care unit; IPF: idiopathic pulmonary fibrosis; MCA: middle cerebral artery; NA: not assessed; NASH: nonalcoholic steatohepatitis; ND: non-diagnostic; Neg: negative; PAD: peripheral artery disease; PE: pulmonary embolism; SAH: subarachnoid hemorrhage; Pos: positive; s/p: status post; VSD: ventricular septal defect.

**eTable 2. Scoring criteria for axon and microvascular pathology**

| <b>Axon Pathology Scoring</b>        |  |
|--------------------------------------|--|
| 1                                    | Minimal to mild axon degeneration: Mild unfolding of myelin sheath, slight accumulation of organelles  |
| 2                                    | Moderate axon degeneration: Moderate structural disruption, mild vacuolar changes in myelin sheath   |
| 3                                    | Severe axon degeneration: Major structural disruption, severe vacuolar changes in myelin sheath, presence of lysosomes, abundant myelin fragmentation and debris |
| <b>Endothelial Pathology Scoring</b> |  |
| 1                                    | Mild to moderate cytoplasmic swelling, mitochondrial injury +/- subendothelial edema   |
| 2                                    | Moderate-severe cytoplasmic swelling, mitochondrial injury +/- subendothelial edema  |
| 3                                    | Obvious rupture of endothelial cells, abundant lysosome accumulation, near complete/complete occlusion of lumen, thrombosis                                      |

**eTable 3. Interobserver reliability in axon and microvascular pathology scoring**

| <b>Overall Agreement on Axon Pathology<sup>a</sup></b> |              |                       |          |                     |   |                    |
|--|--------------|-----------------------|----------|---------------------|---|--------------------|
|  | <b>Kappa</b> | <b>Asymptotic</b>     |          |                     | <b>Asymptotic 95% Confidence Interval</b> |                    |
|  |              | <b>Standard Error</b> | <b>Z</b> | <b>Significance</b> | <b>Lower Bound</b>                        | <b>Upper Bound</b> |
| <b>Overall Agreement</b>                               | .411         | .041                  | 9.893    | .000                | .329                                      | .492               |

a. Sample data contains 112 effective images and 3 raters.

| <b>Overall Agreement on Microvascular Pathology<sup>b</sup></b> |              |                       |          |                     |   |                    |
|---|--------------|-----------------------|----------|---------------------|---|--------------------|
|   | <b>Kappa</b> | <b>Asymptotic</b>     |          |                     | <b>Asymptotic 95% Confidence Interval</b> |                    |
|   |              | <b>Standard Error</b> | <b>Z</b> | <b>Significance</b> | <b>Lower Bound</b>                        | <b>Upper Bound</b> |
| <b>Overall Agreement</b>  | .373         | .032                  | 11.635   | .000                | .310                                      | .436               |

b. Sample data contains 190 effective images and 3 raters.

**eTable 4. No increase in neuroinflammation in olfactory tissue from COVID-19 patients**

| Case No. | Age/Sex | Smell or Taste Dysfunction | CD3+ T Lymphocytes (/HPF) <sup>a</sup> | CD20+ B Lymphocytes | CD68+ Microglia (/HPF) <sup>b</sup> | GFAP+ Reactive Astrocytes <sup>c</sup> |
|----------|---------|----------------------------|--|---------------------|-------------------------------------|--|
| 1        | 30s/F   | Diminished Smell           | Tissue Unavailable                     |                     |                                     |  |
| 2        | 60s/M   | Loss of Smell              | Focal Leptomeningeal                   | None                | NA                                  | Frequent                               |
| 3        | 50s/M   | Loss of Smell              | Scattered (10)                         | None                | 20                                  | Moderate                               |
| 4        | 60s/M   | Loss of Smell              | Focal Perivascular                     | None                | 15                                  | Sparse                                 |
| 5        | 50s/M   | Loss of Smell & Taste      | Tissue Unavailable                     |                     |                                     |  |
| 6        | 20s/M   | Loss of Smell & Taste      | Scattered (5)                          | None                | 33                                  | Moderate                               |
| 7        | 60s/F   | Diminished Smell           | Scattered (4) and Focal Perivascular   | None                | 30                                  | Moderate                               |
| 8        | 40s/M   | Diminished Smell           | Tissue Unavailable                     |                     |                                     |  |
| 9        | 70s/M   | Diminished Smell           | Rare                                   | Rare                | 12                                  | Frequent                               |
| 10       | 80s/F   | None                       | Rare                                   | None                | 58                                  | Moderate                               |
| 11       | 60s/F   | None                       | Rare                                   | None                | 22                                  | Sparse                                 |
| 12       | 40s/M   | None                       | Rare                                   | None                | 12                                  | Moderate                               |
| 13       | 60s/M   | None                       | Rare                                   | None                | 22                                  | Moderate                               |
| 14       | 40s/F   | None                       | None                                   | None                | 12                                  | None                                   |
| 15       | 60s/M   | None                       | Tissue Unavailable                     |                     |                                     |  |
| 16       | 90s/M   | None                       | Focal Perivascular                     | NA                  | 10                                  | Frequent                               |
| 17       | 60s/M   | None                       | Tissue Unavailable                     |                     |                                     |  |
| 18       | 80s/F   | None                       | Scattered (10)                         | None                | 17                                  | Frequent                               |
| 19       | 60s/M   | None                       | Tissue Unavailable                     |                     |                                     |  |
| 20       | 50s/F   | None                       | Scattered (5)                          | Very Rare           | 29                                  | Frequent                               |
| 21       | 70s/F   | None                       | Scattered (3)                          | None                | 24                                  | Moderate                               |
| 22       | 30s/F   | Unknown                    | None                                   | None                | Rare                                | None                                   |
| 23       | 30s/M   | Unknown                    | Rare                                   | None                | 15                                  | Sparse                                 |
| 1C       | 50s/F   | None                       | Scattered (5)                          | None                | 30                                  | Moderate                               |
| 2C       | 60s/M   | None                       | Scattered (3)                          | None                | 18                                  | Frequent                               |
| 3C       | 50s/F   | None                       | Focal Clustered (30)                   | None                | 20                                  | Frequent                               |
| 4C       | 70s/M   | None                       | Tissue Unavailable                     |                     |                                     |  |
| 5C       | 20s/F   | None                       | Rare                                   | None                | 5                                   | Moderate                               |
| 6C       | 30s/M   | None                       | Tissue Unavailable                     |                     |                                     |  |
| 7C       | 20s/M   | None                       | Rare                                   | None                | 23                                  | Moderate                               |
| 8C       | 60s/M   | None                       | Tissue Unavailable                     |                     |                                     |  |

**eTable S4. No increase in neuroinflammation in olfactory tissue from COVID-19 patients (continued)**

| Case No. | Age/Sex | Smell or Taste Dysfunction | CD3+ T Lymphocytes (/HPF) <sup>a</sup> | CD20+ B Lymphocytes | CD68+ Microglia (/HPF) <sup>b</sup> | GFAP+ Reactive Astrocytes <sup>c</sup> |
|----------|---------|----------------------------|--|---------------------|-------------------------------------|--|
| 9C       | 40s/F   | None                       | Scattered (10) and Perivascular        | None                | 18                                  | Moderate                               |
| 10C      | 20s/F   | None                       | NA                                     | None                | NA                                  | Moderate                               |
| 11C      | 40s/M   | None                       | Tissue Unavailable                     |                     |                                     |  |
| 12C      | 50s/M   | None                       | Tissue Unavailable                     |                     |                                     |  |
| 13C      | 60s/F   | None                       | Focal Perivascular                     | Rare                | 55                                  | Frequent                               |
| 14C      | 70s/F   | None                       | Focal Perivascular                     | None                | 24                                  | Frequent                               |

a. Represents an average of the 3 most dense areas

b. Represents an average of the 3 most dense areas; May contain macrophages

c. Precise quantification is impossible due to intense background staining from astrocytes and oligodendrocytes

GFAP: Glial fibrillary acidic protein; HPF: High-power field; NA: Not assessed

**eTable 5. No significant tau deposits in olfactory or brain tissue from COVID-19 patients**

| Case No. | Age/Sex | Smell or Taste Dysfunction | NFT in Olfactory Tissue | NFT (Braak) Staging in Brain | AD Neuropathologic Change   |
|----------|---------|----------------------------|-------------------------|------------------------------|-----------------------------|
| 1        | 30s/F   | Diminished Smell           | Tissue Unavailable      | NA                           | NA                          |
| 2        | 60s/M   | Loss of Smell              | Sparse                  | II                           | Low Level (A2B1C2)          |
| 3        | 50s/M   | Loss of Smell              | Sparse                  | 0                            | Not (A0B0C0)                |
| 4        | 60s/M   | Loss of Smell              | None                    | II                           | Not (A0B1C0)                |
| 5        | 50s/M   | Loss of Smell & Taste      | Tissue Unavailable      | I                            | Not (A0B1C0)                |
| 6        | 20s/M   | Loss of Smell & Taste      | None                    | NA                           | NA                          |
| 7        | 60s/F   | Diminished Smell           | Moderate                | III                          | Low Level (A1B2C1)          |
| 8        | 40s/M   | Diminished Smell           | Tissue Unavailable      | 0                            | Not (A0B0C0)                |
| 9        | 70s/M   | Diminished Smell           | Sparse                  | IV                           | Not (A0B2C0)                |
| 10       | 80s/F   | None                       | Frequent                | V                            | Intermediate level (A2B3C2) |
| 11       | 60s/F   | None                       | Sparse                  | II                           | Not (A0B1C0)                |
| 12       | 40s/M   | None                       | None                    | 0                            | Not (A0B0C0)                |
| 13       | 60s/M   | None                       | None                    | 0                            | Not (A0B0C0)                |
| 14       | 40s/F   | None                       | None                    | 0                            | Not (A0B0C0)                |
| 15       | 60s/M   | None                       | Tissue Unavailable      | 0                            | Low Level (A1B0C0)          |
| 16       | 90s/M   | None                       | Frequent                | III                          | Low level (A1B2C1)          |
| 17       | 60s/M   | None                       | Tissue Unavailable      | 0                            | Not (A0B0C0)                |
| 18       | 80s/F   | None                       | Moderate                | II                           | Low level (A1B1C1)          |
| 19       | 60s/M   | None                       | Tissue Unavailable      | Tissue Unavailable           | Tissue Unavailable          |
| 20       | 50s/F   | None                       | None                    | 0                            | Not (A0B0C0)                |
| 21       | 70s/F   | None                       | Sparse                  | II                           | Not (A0B1C0)                |
| 22       | 30s/F   | Unknown                    | None                    | NA                           | NA                          |
| 23       | 30s/M   | Unknown                    | None                    | NA                           | NA                          |
| 1C       | 50s/F   | None                       | Sparse                  | 0                            | Not (A0B0C0)                |
| 2C       | 60s/M   | None                       | Sparse                  | 0                            | Not (A0B0C0)                |
| 3C       | 50s/F   | None                       | Sparse                  | 0                            | Not (A0B0C0)                |
| 4C       | 70s/M   | None                       | Tissue Unavailable      | III                          | Not (A0B2C0)                |
| 5C       | 20s/F   | None                       | None                    | NA                           | NA                          |
| 6C       | 30s/M   | None                       | Tissue Unavailable      | NA                           | NA                          |
| 7C       | 20s/M   | None                       | None                    | NA                           | NA                          |
| 8C       | 60s/M   | None                       | Tissue Unavailable      | I                            | Not (A0B1C0)                |
| 9C       | 40s/F   | None                       | None                    | 0                            | Not (A0B0C0)                |
| 10C      | 20s/F   | None                       | None                    | NA                           | NA                          |
| 11C      | 40s/M   | None                       | Tissue Unavailable      | 0                            | Low level (A1B0C0)          |
| 12C      | 50s/M   | None                       | Tissue Unavailable      | V                            | Intermediate Level (A1B3C2) |

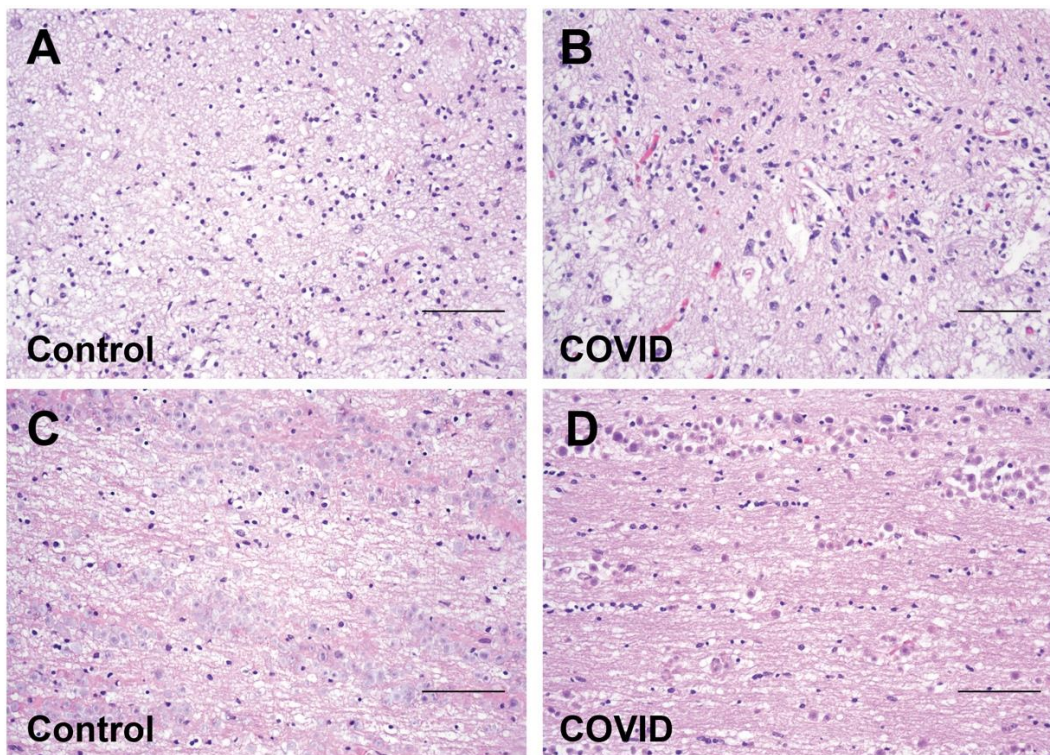


**eTable 5. No significant tau deposits in olfactory or brain tissue from COVID-19 patients (continued)**

| Case No. | Age/Sex | Smell or Taste Dysfunction | Tau Deposits in Olfactory Tissue | NFT (Braak) Staging in Brain | AD Neuropathologic Change |
|----------|---------|----------------------------|----------------------------------|------------------------------|---------------------------|
| 13C      | 60s/F   | None                       | Sparse                           | II                           | Not (A0B1C0)              |
| 14C      | 70s/F   | None                       | Sparse                           | II                           | Low level (A1B1C1)        |

AD: Alzheimer disease; NA: Not assessed; NFT: Neurofibrillary tangles

**eFigure 1. COVID-19 olfactory bulb and olfactory tract are unremarkable on routine histological examination.**



Panels A and B are hematoxylin and eosin (H&E)-stained histological sections of olfactory bulb from a control individual (Case 2C) and a COVID-19 patient (Case 2), respectively. Panels C and D are histological images of olfactory tract from the same control and COVID-19 individuals. Note that there is a lack of inflammation and viral cytopathic effect in the COVID-19 olfactory tissue. The purplish spherical bodies in olfactory tract are corpora amylacea, which is a normal structure in both control and COVID-19 cases. Scale bars represent 50  $\mu$ m.

**eFigure 2. Multiple linear regression analysis assessing the effect of age on the following olfactory pathologic features: (A) Axon pathology (B) Axon density, and (C) Microvascular pathology**

