Neurological Complications in COVID-19 Patients: Can Analysis of Specific Antibodies and Viral RNA in Paired Cerebrospinal Fluid and Serum be Used for Accurate Diagnosis of SARS-CoV-2 Neuroinflammatory Disease? A Case Series

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ABSTRACT

BACKGROUND: Neurological complications during and after SARS-CoV-2 infection have been frequently described. The detection of either SARS-CoV-2 RNA or specific antibodies against SARS-CoV-2 in cerebrospinal fluid in the context of concomitant neurological manifestations indicates neuroinfection.

METHODS AND RESULTS: This is a retrospective descriptive analysis of cerebrospinal fluids and serum samples from 2 hospitalized patients and autopsy findings from 2 patients who died at home. Samples were analysed by 3 independent enzyme-linked immunosorbent assays. Specific antibodies against SARS-CoV-2 were detected in cerebrospinal fluids and paired serum in all 4 cases. Levels of antibodies in cerebrospinal fluids were highest in samples from a deceased man with critical progression of COVID-19 and detectable SARS-CoV-2 viral RNA in cerebrospinal fluid, serum, 4 brain biopsies and 15 additional tissue samples, though immunohistochemical staining for SARS-CoV-2 in brain tissue did not detect the virus.

CONCLUSION: Detection of SARS-CoV-2 antibodies in paired serum and cerebrospinal fluid may support the presence of SARS-CoV-2 neuroinflammatory disease in patients with COVID-19 and neurological manifestations.

KEYWORDS: Antibodies, autopsy, case reports, coronavirus, immunohistochemistry, SARS virus

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has the potential for neurological disease in humans and animals.1-4 The current aetiological hypothesis is that the virus triggers an inappropriate immune response which injures neurones and terminates contact between them.5,6 The detection of either SARS-CoV-2 RNA or specific antibodies against SARS-CoV-2 in cerebrospinal fluid (CSF) in the context of concomitant neurological manifestations indicates neuroinfection. However, PCR analyses for SARS-CoV-2 RNA in CSF are often negative in patients with neurological symptoms.7,8 Indirect evidence of neurological infection with SARS-CoV-2 can be established by the detection of SARS-CoV-2 specific antibodies in CSF.9 Moreover, the measurement of specific antibody responses in CSF has a
higher predictive value for neurological damage compared to biomarkers, such as total-tau protein and glial fibrillary acidic protein. Knowledge regarding the clinical presentations of COVID-19 associated neurological disease is still limited. We present 4 patients with moderate to severe new-onset neurological symptoms developed less than 6 weeks after SARS-CoV-2 infection and with detectable SARS-CoV-2 specific antibodies in CSF. The information was gathered from medical records, police records and autopsy reports.

Case Presentations

Case 1

A 32-year old man, previously living in Copenhagen, with a history of obesity (BMI 44.4) and untreated hypertension was found dead in his apartment in December 2020 (Table 1). The last known contact was the day before. During isolation due to a positive PCR test for SARS-CoV-2, he had reported fatigue, dizziness and difficulties sleeping and walking.

Post-mortem CT-scan (PMCT) showed bilateral consolidation of the lung tissue with extensive, evenly distributed ground glass opacities and traction bronchiectasis in both upper lobes. PMCT of the brain was unremarkable.

The autopsy revealed brain oedema with slight flattening of the gyri. The brain weighed 1860 g (normal weight 1250 ± 20 g). On gross examination there were no macroscopic signs of inflammation in the meninges or the brain tissue. The lungs were heavily congested and oedematous with diffuse consolidation. Total weight of the lungs was 1826 g (normal weight 840 g; upper limit of normal 1300 g). The lung tissue was generally hyperaemic. Extensive histological sampling from the brain and lungs (formalin-fixed and paraffin-embedded, FFPE) were examined using histochemical stains. Brain samples were further examined using immunohistochemical stains. Tissue examined from the brain and the lungs is listed in Supplemental Table S2. There were no microscopic signs of inflammation, necrosis, thrombosis or haemorrhage in the leptomeninges or in the brain parenchyma. Immunohistochemistry staining for SARS-CoV-2 were negative in all tested areas from the brain. The histopathology of the lung tissue revealed bilateral consolidation caused by severe acute inflammation with neutrophile granulocytes, macrophages, hyaline membranes and type 2 pneumocytes hyperplasia. Interstitial organization was seen locally. There were diffuse foci of pneumonia in the left lung. The lung tissue was generally hyperaemic and densified. The lymph nodes were enlarged (>1.5 cm). Extensive histological sampling was undertaken, and tissue slides from the brain and the lungs were examined using histochemical and immunohistochemical stains as previously described in Case 1 (Supplemental Table S2). The tissue-sections of the brain showed chronic changes in accordance with microcephaly. There were no signs of inflammation, necrosis, thrombosis or haemorrhage. Immunohistochemistry for SARS-CoV-2 were negative in all tested areas from the brain. The histopathology of the lung tissue revealed bilateral consolidation caused by severe acute inflammation with neutrophile granulocytes, macrophages, haemorrhage and local necrosis compatible with superimposed acute diffuse bacterial pneumonia.

Toxicologic analysis detected the seizure medication Rufinamide in therapeutic concentration and low therapeutic concentration of paracetamol.

Case 2

A 4-year-old boy from Copenhagen with WDR81 mutation resulting in severe disabilities including microcephaly, mental retardation, epilepsy, reduced muscle tension and chronic respiratory insufficiency managed with Continuous Positive Airway Pressure several times a day (Table 1). He had a history of recurrent pneumonia, most recently a viral pneumonia 2 months prior to his death. He tested positive for SARS-CoV-2 RNA 1 month before his death and had an unremarkable follow-up evaluation around 2 weeks later. One week before his death, he had an epileptic seizure, but was not seen by a paediatrician. He subsequently developed fever, fatigue and anorexia, which was managed as an uncomplicated non-COVID-19 related viral infection not requiring hospitalization. He died while sleeping the same day in the end of January 2021.

Post-mortem CT-scan (PMCT) of the brain showed bilateral extensive expanded ventricles and atrophic grey and white matter. The pulmonary PMCT demonstrated peripheral ground-glass opacities in the lower right lobe. The upper left lobe had 2 atelectatic areas.

The autopsy revealed microcephaly with particularly reduced frontal lobes compared to the other lobes. The ventricles were dilated. There were no signs of inflammation in the meninges or the brain tissue. The lungs had a total weight of 288 g (normal weight 105 g; upper limit of normal 425 g). There were diffuse foci of pneumonia in the left lung. The lung tissue was generally hyperaemic and densified. The lymph nodes were enlarged (>1.5 cm). Extensive histological sampling was undertaken, and tissue slides from the brain and the lungs were examined using histochemical and immunohistochemical stains as previously described in Case 1 (Supplemental Table S2). The tissue-sections of the brain showed chronic changes in accordance with microcephaly. There were no signs of inflammation, necrosis, thrombosis or haemorrhage. Immunohistochemistry for SARS-CoV-2 were negative in all tested areas from the brain. The histopathology of the lung tissue revealed bilateral consolidation caused by severe acute inflammation with neutrophile granulocytes, macrophages, haemorrhage and local necrosis compatible with superimposed acute diffuse bacterial pneumonia.

Toxicologic analysis detected the seizure medication Rufinamide in therapeutic concentration and low therapeutic concentration of paracetamol.

Case 3

A 79-year-old woman (see Table 1 for details) with nonconvulsive status epilepticus was diagnosed with Herpes simplex virus 1 (HSV-1) encephalitis in December 2020 at North Zealand Hospital Emergency Department. The diagnosis was based on positive CSF PCR, mesial temporal lobe Fluid-attenuated inversion recovery (FLAIR) hyperintensities on brain Magnetic Resonance Imaging (MRI), and electroencephalogram (EEG) findings. Treatment included intravenous (i.v.) aciclovir 10 mg/kg 8 hour for 12 days and anticonvulsive therapy. The patient developed clinical, biochemical and radiological signs of pneumonia on day 8 of hospitalization, and SARS-CoV-2 RNA was detected in tracheal aspirate. Remdesivir 200 mg followed by
100 mg once daily for 4 days and dexamethasone 8 mg once daily for 6 days were administrated. The patient was discharged in good general condition on day 16 after hospitalization. Nine days after discharge she was readmitted febrile with a Glasgow Coma Scale (GCS) of 12 and rattling respiration. A lumbar puncture (LP) was performed, and CSF analysis revealed

| N | CASE 1 | CASE 2 | CASE 3 | CASE 4 |
|---|--------|--------|--------|--------|
| **Demographic data** | | | | |
| Age (years) | 33 | 4 | 79 | 61 |
| Sex (M/F) | M | M | F | M |
| BMI (kg/m²) | 44 | NA | 26 | 25 |
| Ethnicity | Caucasian | Hispanic | Hispanic | Middle Eastern |
| **Comorbidities** | | | | |
| Hypertension | Yes | No | Yes | No |
| Diabetes mellitus | No | No | No | No |
| Coronary artery disease | No | No | No | No |
| Autoimmune disease | No | No | No | No |
| Smoking status (current or former) | No | No | No | Yes |
| Anatomical and functional brain abnormalities | No | Yes | Yes | No |
| **COVID-19 associated neurological manifestations** | | | | |
| Neurological syndrome | Insufficient data | Insufficient data | Encephalitis (level 1) | Myelitis (level 1) |
| Time period between positive SARS-CoV-2 RT-PCR test (oropharyngeal swab/tracheal aspirate) and onset of neurological symptoms (days) | NA | NA | 7 | 19 |
| Time period between positive SARS-CoV-2 RT-PCR test (oropharyngeal swab/tracheal aspirate) and death (days) | 14 | 30 | 30 | NA |
| **Preliminary CSF analysis** | | | | |
| Pleocytosis (>5 × 10⁶/L) | NA | NA | Yes | Yes |
| Mononuclear cells: Nucleated cell count: | | | 72 × 10⁶/L | 9 × 10⁶/L |
| Elevated protein (>0.5 g/L) | NA | NA | Yes | No |
| Elevated IgG index (>0.60) | NA | NA | NA | Yes |
| Oligoclonal bands | NA | NA | NA | Yes |
| Red blood count (>300 × 10⁶/L) | NA | NA | No | No |
| **Neuroimaging** | | | | |
| Brain MRI with contrast | NA | NA | Temporal lobe FLAIR hyperintensities | - |
| Spine MRI with contrast | NA | NA | Old lacunar infarct | - |
| PMCT | - | Hydrocephalus | White and grey matter atrophy | NA |

Abbreviations: NA, not available; PMCT, post-mortem CT-scan. 
*~*: negative.
mononuclear pleocytosis \((72 \times 10^6/L <5 \times 10^6/L)\), elevated protein \(0.68 g/L [0.15-0.50 g/L]\), lactate \(2.7 mmol/L [1.1-2.4 mmol/L]\) and erythrocytes \(2000 \times 10^6/L <3000 \times 10^6/L]\). Insufficient treatment of HSV-1 encephalitis and nosocomial pneumonia were suspected. Aciclovir 10 mg/kg 8-hourly and Piperacillin/Tazobactam 4 g/0.5 g 6 hourly were initiated upon admission. EEG findings were consistent with mild encephalopathy. On the third day of hospitalization, brain MR angiography showed progression of cortical hyperintensities on FLAIR sequences in the right mesial temporal lobe. LP, brain MRI and EEG were repeated on the 10th day of hospitalization without new significant findings. Autoimmune encephalitis antibodies in serum (CASP2Ab, LGI1-Ab, NMDAR1-Ab, GABA-B-receptor-1-Ab, Glutamate receptor-1-Ab, GABA-A receptor-2-Ab, Gad65-Ab) and CSF (CASP2Ab, LGI1-Ab, NMDAR1-Ab, GABA-B-receptor-1-Ab, Glutamate receptor-1-Ab, Glutamate-receptor-2-Ab, Gad65-Ab) were negative. The patient’s clinical condition deteriorated with multiorgan failure, and she died on day 12. Retrospective analyses of CSF and serum are presented in Table 2.

### Case 4

A 61-year-old man (see Table 1 for details) with symptoms of upper respiratory infection and a positive SARS-CoV-2 RT-PCR test on oropharyngeal swab. Symptoms resolved without treatment but 19 days after symptom onset, he presented at the emergency department with urinary retention, constipation, bilateral lower limb weakness and paraesthesia. Clinical examination performed in February 2021 at North...
Zealand Hospital Emergency Department revealed hyporeflexia and weakness of the lower limbs, partial loss of sensitivity below the Th10 level and decreased anal sphincter tone. Upon admission, SARS-CoV-2 RT-PCR test on a tracheal aspirate was positive. A lumbar puncture was performed on the third day of hospitalization and CSF analysis revealed mononuclear pleocytosis ($9 \times 10^6/L < 5 \times 10^6/L$), an elevated IgG index and oligoclonal bands. No paraneoplastic antibodies (Amphilphysin-Ab, CDR2-Ab, DRP-5-Ab, Hu-Ab, PNMA2-Ab, NOVA1-Ab, GAD65-Ab, Recoverin-Ab, SOX-1-Ab, DNER-Ab, Zic-4-Ab, Titin-Ab) or autoantibodies of systemic autoimmune disease (ANA, DNA-ds-Ab, Scl-70-Ab, Jo1-Ab, CENP-B-Ab, SSA-Ab, SSB-Ab, Smiths-Ab, U1-snRNP-Ab, AQP4-Ab, MOG-Ab, Beta-2-GP1-Ab, Cardiolipin-IgG) were detected in serum except for cardiolipin IgM ($24 \times 10^6$/IU/L $< 10^6$/IU/L). MRI of the brain and spine with i.v. contrast was normal. Somatosensory evoked potentials (SSEPs) and motor evoked potentials (MEPs) revealed prolonged central conduction times. Electromyography (EMG) was normal. Four days after onset of neurological symptoms, treatment with i.v. methylprednisolone 1 g once daily for 5 days was initiated for presumed acute transversal myelitis. After 2 weeks of hospitalization lower limb weakness progressed and intravenous immunoglobulin 0.4 g/kg once daily was administered for 5 days, and prednisolone treatment 75 mg once daily was initiated. MRI of the spine was repeated during hospitalization without significant findings. The patient was discharged after 41 days; neurological status had only improved slightly during hospitalization.

**Other Microbiological Investigations**

The qualitative Wantai SARS-CoV-2 Total Antibody ELISA (Beijing Wantai Biological Pharmacy Enterprise), and the quantitative assays, the anti-SARS-CoV-2 QuantiVac ELISA (IGG) (Euroimmun Medizinische Labordiagnostika AG) and solid phase ELISA, DRG SARS-CoV-2 (RBD) IgG ELISA (DRG International) kits were used for measuring anti-SARS-CoV-2 antibodies in CSF and paired serum samples according to the manufacturers’ instructions (Table 2). The Wantai assay is based on a double-antigen sandwich principle that detects total antibodies binding to the SARS-CoV-2 spike protein receptor binding domain. IgG antibodies against SARS-CoV-2 spike protein subunit 1 were detected by the assay from EUROIMMUN and DRG.

Case 3 tested positive for SARS-CoV-2 RNA in tracheal aspirate on day 8 of hospitalization. Case 2 and 4 tested positive for SARS-CoV-2 RNA on oropharyngeal swabs at symptoms onset. Case 1 was positive for SARS-CoV-2 RNA on oropharyngeal swab collected during the autopsy. A total of 32 biopsy samples for each of Case 1 and 2 were analysed with SARS-CoV-2 RT-PCR. Only Case 1 was positive for SARS-CoV-2 RNA in CSF with a cycle threshold (Ct) of 38 and in serum with a Ct of 37. From Case 1, 19 of 32 biopsies were positive (Supplemental Table S1). Furthermore, we detected SARS-CoV-2 RNA in 3 of 7 brain biopsies (olfactory bulb, pons, orbital frontal cortex) from Case 1.

Whole genome sequencing (WGS) was performed on tracheal aspirate for Case 3 and on oropharyngeal swab for Case 1 and 4. Sequencing of sample for Case 2 was not successful due to the low amount of RNA in the specimen. SARS-CoV-2 sequencing was performed by extracting RNA from the specimens using RNAvanced (Beckman Coulter, Pasadena, CA, USA). According to the manufacturer’s instructions, the Sequencing libraries were prepared using all reagents included COVIDSeq Test RUO (Illumina, San Diego, CA, USA). Briefly, in batches of 384 samples, the COVID-19 Genomes were PCR amplified in 2 reactions according to the ARTIC version 3 schema. Combined before library prep using the DNA prep module, the libraries were then indexed using unique dual index before being bead normalized and pooled. The pool was normalized and sequenced using paired-end reads 74bp long. Based on the WGS-data analysis, both isolates from Cases 3 and 4 were from the same 20A.EU2 clade B1.160 lineage by the classification system implemented.11 The isolate for Case 1 belonged to the 20I/501Y.V1 clade and B.1.1.7 with deletion 69–70 in spike protein.

**Other microbiological results:** The first CSFs from Cases 3 and 4 were tested with BioFire FilmArray (BioFire Diagnostics, LLC, Salt Lake City, Utah, USA). Case 4 tested negative and Case 3 tested positive for HSV-1. Case 3 had no detectable intrathecal production of antibodies for HSV-1 upon admission but tested positive at the time of readmission. Additionally, CSF and serum samples from Case 4 were examined for intrathecal antibody production due to neuroborreliosis, neurosyphilis, Tick Borne Encephalitis, HSV, and Varicella Zoster Virus, and all were negative. Case 4 also tested negative for HIV in a screening test.

All 4 lung biopsies from Cases 1 and 2 were tested negative for 17 respiratory tract viruses (influenza type A and B, respiratory syncytial virus type A and B, metapneumovirus, parainfluenzavirus type 1–4, adenovirus, rhinovirus, enterovirus, parechovirus, and coronavirus OC43, 229E, NL63, HKU1).

**Discussion and Conclusion**

We describe 4 patients' phenotypes related to moderate to severe new-onset neurological symptoms developed less than 6 weeks after acute COVID-19 infection. In all 4 cases the presence of the specific SARS-CoV-2 antibodies was detected in CSF indicating CNS involvement with SARS-CoV-2. All 4 cases met the criteria suggested for COVID-19 associated neurological disease, and were defined as possible cases.12 Direct viral invasion of the CNS remains controversial as the presence of SARS-CoV-2 RNA does not equate to viral replication in the CNS. The mechanisms of potential SARS-CoV-2-associated neuroinvasion are hypothesized to occur either directly by axonal transport via olfactory and trigeminal nerves or haematogenously through a disrupted blood-brain barrier.
In the brain tissue-sections examined from Case 1 we detected no signs of inflammation, necrosis, thrombosis or haemorrhage despite the presence of the SARS-CoV-2 RNA in the biopsy samples from the olfactory bulb, orbital frontal cortex and pond. Experimental mice model infected with SARS-CoV-2 have shown no or minimal signs of inflammation in SARS-CoV-2 infected brain-tissue even with widespread infection suggesting the possibility of neurotoxicity associated with minimal inflammatory response. We cannot rule out that the lack of pathological findings could be ascribed to the anatomical sampling of tissue, and that pathological findings were present in other parts of the brain. Moreover, a case-control study from the UK showed greater changes in the orbitofrontal cortex using MRI among cases tested positive for SARS-CoV-2. A significant reduction in grey matter thickness was observed, also among patients with mild cases of COVID-19 infection.

The specific SARS-CoV-2 antibodies were determined in the CSF's and corresponding blood sample from all 4 patients using 3 SARS-CoV-2-specific ELISA assays. WANTAI Total Antibody ELISA and EUROIMMUN IgG ELISA have been externally validated for the detection of antibodies in serum. So far, none of the assays have been validated for use on CSF. Overall, data suggest that all 3 assays can be used on CSF with adjustment of cut-off and determination of essential dilution, although further validation is needed.

CSF/serum IgG ratio was calculated for all 4 patients and was the highest for Case 1, a deceased man with critical progression of COVID-19, detectable SARS-CoV-2 viral RNA in CSF, serum and 3 brain biopsies. Immunohistochemical staining for SARS-CoV-2 did not detect the virus in tissue-sections from the brain which might be attributed to viral load below the sensitivity for immunohistochemistry and/or the FFPE preparation had changed the sensitivity. Brain autopsy studies in the context of COVID-19 are limited and report different pathological findings, for example, hypoxic brain injury, lymphatic encephalitis and meningitis and micro-thrombi with infarction.

In Case 3, the serum titre was the highest and in Case 4, both high and low titres were observed on different measurements. CSF/serum albumin index, an indicator for BBB integrity, could only be calculated for Case 4 and indicated intact BBB. Experiments on mice with SARS-CoV-2 brain infection suggest that CNS antibody production is compartmentalized and not a result of passive transfer from the systemic circulation. Further investigations performed on larger collections of specimens including neuropathological investigations are needed to confirm this association. Further studies are needed to validate the utility of different commercial kits for measurement of specific SARS-CoV-2 antibodies in cerebrospinal fluid.
8. Lewis A, Frontera J, Placantonakis DG, et al. Cerebrospinal fluid in COVID-19: a systematic review of the literature. J Neurol Sci. 2021;421:117316.
9. Song E, Bartley CM, Chow RD, et al. Divergent and self-reactive immune responses in the CNS of COVID-19 patients with neurological symptoms. Cell Reports Med. 2021;2:100288.
10. Cunningham JL, Virhammar J, Rönnberg B, et al. Anti-SARS-CoV2 antibody responses in serum and cerebrospinal fluid of COVID-19 patients with neurological symptoms. J Infect Dis. 2021;225:1-18.
11. Aksamentov I, Roemer C, Hodcroft E, Neher R. Nextclade: clade assignment, mutation calling and quality control for viral genomes. J Open Source Softw. 2021;6:3773.
12. Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. Lancet Neurol. 2020;19:767-783.
13. Li Z, Liu T, Yang N, et al. Neurological manifestations of patients with COVID-19: potential routes of SARS-CoV-2 neuroinvasion from the periphery to the brain. Front Med. 2020;14:533-541.
14. Zhou P, Yang XL, Wang XG, et al. Addendum: a pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;588:E6-273.
15. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J Virol. 2008;82:7264-7275.
16. Douaud G, Lee S, Alfaro-Almagro F, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature. 2022;604:697-707.
17. Harritschaj LH, Gybel-Brask M, Afsal S, et al. Comparison of sixteen serological SARS-CoV-2 immunoassays in sixteen clinical laboratories. J Clin Microbiol. 2020;59:e02596-20.
18. Lassaunière R, Friache A, Harboe ZB, et al. Evaluation of nine commercial SARS-CoV-2 immunoassays. medRxiv. 2020;20056325.
19. Meenter T, Haibauer JD, Nierhof R, et al. 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. Histopathology. 2020;77:198-209.
20. von Weyhern CH, Kaufmann I, Neff F, Kremer M. Early evidence of pronounced brain involvement in fatal COVID-19 outcomes. Lancet. 2020;395:e109.
21. Bryce C, Grimes Z, Pujadas E, et al. Pathophysiology of SARS-CoV-2: the Mount Sinai COVID-19 autopsy experience. Mod Pathol. 2021;34:1456-1467.
22. Obermeier B, Daneman R, Ransohoff RM. Development, maintenance and disruption of the blood-brain barrier. Nat Med. 2013;19:1584-1596.
23. Tibbling G, Link H, Ohman S. Principles of albumin and IgG analyses in neurological disorders. I. Establishment of reference values. Scand J Clin Lab Invest. 1977;37:385-390.
24. Hennington MJ, Khattar-Lashgari A, Olsen KB, Jacobsen C, Brochner CB, Banner J. Translational deep phenotyping of deaths related to the COVID-19 pandemic: Protocol for a prospective observational autopsy study. BMJ Open. 2021;11:e049083-10.