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Dear Editor,

Neurological symptoms in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are common [1]. SARS-CoV-2-RNA was detected by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) in very few cases in cerebrospinal fluid (CSF) [2] as well as virus particles in autopsy brain samples in single cases [3]. This has prompted an ongoing controversy whether neurological symptoms are caused by viral infection of the CNS or via other mechanisms.

We report the neurologic features along with CSF analysis findings in an observational series of 30 COVID-19 patients admitted to six tertiary referral centers in Germany from March until June 2020 as a selection from the register study PANDEMIC (Pooled Analysis of Neurologic DisordErs Manifesting in Intensive care of COVID-19).

Frequent neurologic symptoms were altered mental state (10; 33.3%), new paresis (9; 30.0%), impaired consciousness (7; 23.3%), hypo-/areflexia (9; 30.0%), anosmia/hyposmia or ageusia/hypogeusia (6; 20.0%, underreported in critical care patients) and seizures (5; 16.7%) (Table 1). Frequent neurologic diagnoses were encephalopathy (11; 36.7%), cerebrovascular events (5; 16.7%), and (poly)neuropathy (9; 30.0%) including one Miller-Fisher syndrome and two Guillain-Barré syndromes.

15 patients underwent lumbar puncture (LP) during critical disease phases (definitions in supplemental material), one during a complicated, 13 during uncomplicated and one during recovery phases of COVID-19. The time between positive SARS-CoV2-PCR e.g. from oropharyngeal swab and LP was 5.9 ± 9.8 days (median 1; range 0–35 days; patients with additional positive SARS-CoV-2-PCRs after LP were counted as 0 days). Their CSF showed normal or slightly increased white blood cell count (WBC) (≤8/μl) in 28 cases, while the WBC was significantly elevated in two patients with herpes simplex virus 1 encephalitis and intracranial hemorrhage (Fig. 1). The CSF blood albumin ratio as a marker for the blood-CSF integrity was normal in most cases (14/25) nevertheless, five had a severe disruption. Of interest five of seven patients with severe or intermediate blood-CSF disruption received LP during critical disease phase.

Oligoclonal bands were negative in 14 of 25 tested cases (56.0%), in ten cases we found identical oligoclonal bands in CSF and serum (40.0%) and in the case of HSVE oligoclonal bands in CSF and serum with additional bands in CSF (40%) were detected. In all 30 cases, RT-PCR for SARS-CoV-2 from CSF was negative.

Our clinical findings are in concordant with several other reports of autoimmune neuropathies [4], the prevalence of cerebrovascular events [5] and the frequent occurrences of encephalopathies in patients with COVID-19. Cerebrovascular events might be explained by an endotheliitis during COVID-19 [6] and autoimmune neuropathies also argue rather for an indirect affection of the nervous system by parainfectious immune phenomena than direct involvement of the nervous system. A recently published case of encephalopathy with significant increase of interleukin-6 (IL-6) in CSF and clinical response to methylprednisolon without detection of SARS-CoV-2 in CSF supports the theory of an autoimmune mediated hyperinflammatory process as a mechanism in COVID-19 patients with neurological symptoms suspicious for an involvement of the CNS [7].

The absence of CSF findings specific for actual viral (meningo)encephalitis (e.g. increase WBC count) and lack of detection of SARS-CoV-2 by RT-PCR in the, up to date, largest cohort of COVID-19 patients with neurologic symptoms and LP in COVID-19 patients is another puzzle piece suggesting a more likely indirect affection of the nervous system, besides very rare cases of a possible direct affection by SARS-CoV-2.
### Table 1: Clinical characteristics of 30 patients with COVID-19 and neurologic symptoms.

| Pat No. | Age  | Sex   | COVID19-PCR positive in: | Patient status at time point of LP: | Neurologic symptoms                                      | Neurologic diagnosis                                      |
|---------|------|-------|--------------------------|-----------------------------------|----------------------------------------------------------|----------------------------------------------------------|
| 1       | 81   | Male  | BAL                      | Uncomplicated                      | Hypogeusia, unilateral temporary paresis of leg           | TIA                                                      |
| 2       | 25   | Female| NPS                      | Uncomplicated                      | New headache, nausea with vomiting                       | Cerebral venous sinus thrombosis                         |
| 3       | 48   | Female| BAL                      | Uncomplicated                      | Refractory status epilepticus, declined level of consciousness | Encephalitis with herpes simplex virus 1                |
| 4       | 73   | Female| NPS                      | Uncomplicated                      | Involuntary hyperknesia of left arm and leg               | Suspected post-stroke movement disorder                  |
| 5       | 63   | Male  | BAL                      | Critical                           | Areflexia, horizontal gaze palsy, multiple cranial nerve affection, paresis of the left arm | Miller-Fisher Syndrome                                   |
| 6       | 58   | Male  | BAL                      | Critical                           | Declined level of consciousness and prolonged awakening from sedation, seizures | Encephalopathy with seizures, possibly originating from old ischemic lesion |
| 7       | 75   | Female| NPS                      | Uncomplicated                      | Hyposmia, hypogeusia, confusion, global aphasia, multimodal neglect | Septic encephalopathy DD limbic encephalitis          |
| 8       | 66   | Male  | NPS, BAL                 | Uncomplicated                      | Acute brachio-facial hemiparesis, declined level of consciousness | Intracranial hemorrhage in left ventral basal ganglia |
| 9       | 56   | Male  | OPS, BAL, peripheral blood | Critical                          | Altered mental state, menigism, hyporeflexia            | Encephalopathy, CIP                                     |
| 10      | 41   | Female| OPS                      | Critical                           | Gait disturbance, altered mental state, dysarthria       | Osmotic demyelination syndrome                           |
| 11      | 68   | Male  | BAL, peripheral blood     | Critical                           | Clonic seizure                                           | Seizure                                                 |
| 12      | 64   | Male  | OPS, BAL, peripheral blood | Critical                          | Altered mental state, declined level of consciousness, areflexia | Septic/toxic encephalopathy, CIP                         |
| 13      | 57   | Male  | OPS, BAL                 | Critical                           | Generalized tonic clonic seizures and declined level of consciousness during non-convulsive seizures | Non-convulsive status epilepticus                        |
| 14      | 75   | Male  | OPS, BAL, peripheral blood | Critical                          | Altered mental state; increased muscle tone, tetraparesis, areflexia | Encephalopathy, CIP                                     |
| 15      | 47   | Male  | OPS, BAL, peripheral blood | Critical                          | Tetraplegia, fluctuating altered mental state, suspected menigism, areflexia | Encephalopathy, CIP                                     |
| 16      | 50   | Male  | OPS, BAL                 | Critical                           | Declined level of consciousness, generalized seizures    | Seizures                                                |
| 17      | 51   | Male  | OPS, BAL                 | Critical                           | Altered mental state, discrete menigism                  | Encephalopathy                                           |
| 18      | 65   | Female| OPS                      | Uncomplicated                      | Confusion and altered mental state                       | Septic/metabolic encephalopathy                         |
| 19      | 45   | Male  | OPS                      | Uncomplicated                      | New headache                                             | Unclear headache                                         |
| 20      | 68   | Female| OPS                      | Uncomplicated                      | Altered mental state                                     | Encephalopathy                                           |
| 21      | 81   | Male  | OPS, BAL                 | Critical                           | Altered mental state                                     | Encephalopathy                                           |
| 22      | 48   | Male  | OPS                      | Critical                           | Hyposmia, hypogeusia, unilateral peripheral vestibular dysfunction | Unilateral vestibular neuritis                        |
| 23      | 58   | Female| OPS                      | Uncomplicated                      | Unilateral abducens nerve palsy                          | Unilateral abducens nerve palsy                          |
| 24      | 80   | Male  | OPS                      | Uncomplicated                      | Hyposmia, hypogeusia, saccadic ocular pursuit, gait disorder, short-time memory disturbance | Slight septic encephalopathy                            |
| 25      | 70   | Male  | OPS, BAL                 | Critical                           | Tetraparesis, hyporeflexia, Cheyne-Stokes breathing      | CIP, multiple bilateral embolic ischemic strokes         |
| 26      | 76   | Female| OPS, BAL                 | Critical                           | Declined level of consciousness                          | Prolonged coma                                           |
| 27      | 79   | Female| OPS, BAL                 | Critical                           | Ageusia, tetraparesis, hyporeflexia, declined level of consciousness | Guillain-Barré Syndrome, encephalopathy                  |
| 28      | 28   | Female| OPS                      | Complicated                        | Ageusia, anarthria, unilateral sensorimotor hemiparesis, multimodal neglect | Ischemic stroke due to unilateral MCA occlusion          |
| 29      | 68   | Male  | OPS                      | Uncomplicated                      | Altered mental state, seizures                           | Seizures                                                 |
| 30      | 86   | Female| OPS                      | Recovery                           | Tetraparesis, areflexia, ataxia                          | Guillain-Barré Syndrome                                  |

MCA = Middle Cerebral Artery, BAL = bronchoalveolar lavage, CIP = Critical Illness Polyneuropathy, DD = differential diagnosis, LP = lumbar puncture, NPS = nasopharyngeal swab, OPS = oropharyngeal swab, PCR = polymerase-chain-reaction, TIA = transient ischemic attack.
Our case series demonstrates that SARS-CoV-2 is usually not present in CSF of patients with neurological symptoms arguing against frequent active CNS invasion of the virus. Most neurological symptoms seem to be caused by indirect mechanisms such as cerebrovascular events, encephalopathies and neuropathies due to systemic critical illness and secondary immune phenomena. Reported detection of SARS-CoV-2-RNA or antibodies against the virus in the CSF in very few published cases may even be explained by dysfunction of the blood-CSF barrier or contamination with blood during difficult LP. Nevertheless, like in other virus infections of the brain, a negative PCR-test does not exclude the presence of the virus in the brain tissue. Therefore, further studies on antibodies against SARS-CoV2 in CSF would be useful.

Contributors

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Declaration of Competing Interest

None.

Appendix A. Supplementary data

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Letter to the Editor

Journal of the Neurological Sciences 418 (2020) 117090

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