Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Cerebrospinal fluid findings in COVID-19 patients with neurological symptoms

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Dear Editor,

Neurological symptoms in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are commen [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 (4·0%) 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 occurrents 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.

Abbreviations: PANDEMIC, Pooled Analysis of Neurologic DisordErs Manifesting in Intensive care of COVID-19; IGNITE, **I**nitiative of **G**erman **N**euroIntensive **T**rial **E**ngagement; CSF, cerebrospinal fluid; LP, lumbar puncture; RT-PCR, reverse-transcriptase–polymerase-chain-reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WBC, white blood cell count

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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	NPS	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 hyperkinesia 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, meningism, 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 meningism, 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 meningism	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	Uncomplicated	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.

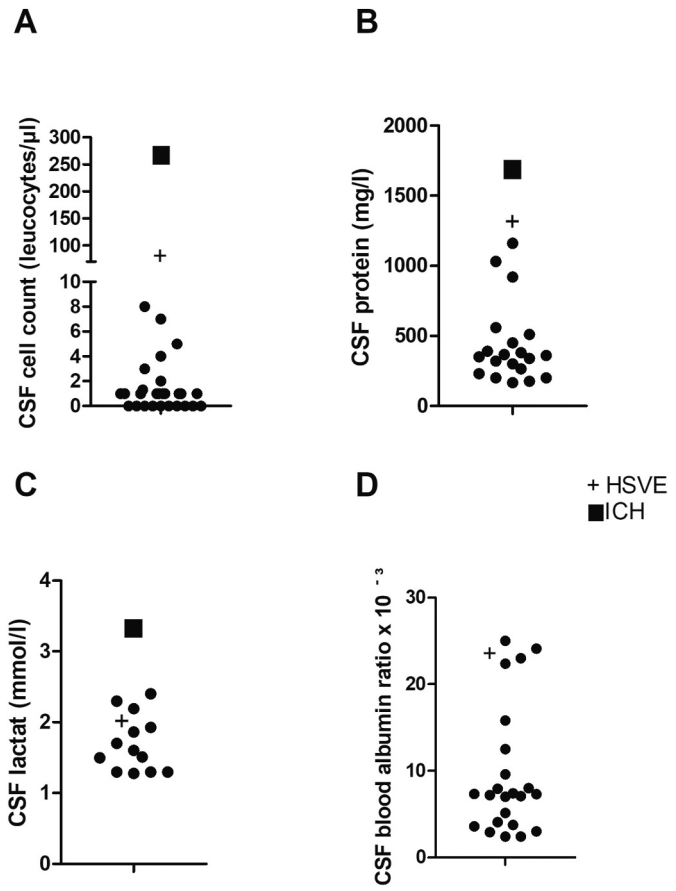

Fig. 1. Cerebrospinal fluid findings in COVID-19 patients with neurological symptoms.
CSF cell count (n = 30) (A), CSF protein levels (n = 23) (B), CSF lactate levels (n = 16) (C) and albumin ratio (n = 25) of patients with COVID-19 infection. Empty dots (circle) are pathological results (A-C). In D grey dots symbolize intermediate blood brain barrier disruption and empty dots (circle) severe blood brain barrier disruption. CSF = cerebrospinal fluid, HSVE = herpes simplex virus encephalitis, ICH = intracranial hemorrhage.

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

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2020.117090.

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