

Cerebrospinal fluid features in COVID-19 patients with neurologic manifestations: correlation with brain MRI findings in 58 patients.

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The study was approved by the ethical committee of Strasbourg University Hospital (CE-2020-37) and was in accordance with the 1964 Helsinki Declaration and its later amendments

Summary : CSF abnormalities were frequent in patients with neurological manifestations related to COVID-19, whereas SARS-CoV 2 detection in CSF remained scanty.

Abstract

Background:

Neurological manifestations are common in patients with COVID-19, but little is known about pathophysiological mechanisms. In this single-center study, we describe neurological manifestations of 58 patients, regarding cerebrospinal fluid (CSF) analysis and neuroimaging findings.

Methods:

58 COVID-19 patients with neurologic manifestations and SARS-CoV-2 RT-PCR screening on CSF analysis were included. Clinical, laboratory, and brain MRI data were retrospectively collected and analyzed.

Results:

Patients were mostly men (66%) with a median age of 62 years. Encephalopathy was frequent (81%), followed by a pyramidal dysfunction (16%), seizures (10%), and headaches (5%). Protein and albumin levels in CSF were increased in 38% and 23%, respectively. A total of 40% of patients displayed an elevated albumin quotient suggesting impaired blood- brain barrier integrity. CSF-specific IgG oligoclonal band was found in five (11%) cases, suggesting an intrathecal synthesis of IgG, and 26 (55%) patients presented identical oligoclonal bands in serum and CSF. Four (7%) patients harbored a positive SARS-CoV-2 RT-PCR in CSF. Regarding brain MRI, 20 (38%) patients presented leptomeningeal enhancement.

Conclusions:

Brain MRI abnormalities, especially leptomeningeal enhancement, and increased inflammatory markers in CSF are frequent in patients with neurological manifestations related to COVID-19, whereas SARS-CoV 2 detection in CSF remained scanty.

Keywords:

COVID-19; Cerebrospinal fluid; Leptomeningeal enhancement

Introduction

In recent months, reports of neurological manifestations in COVID-19 patients have risen (1,2). The underlying mechanisms remain unclear, and there is an unmet need to understand them. On the one hand, some studies suggest that the immune-mediated response to SARS-CoV-2 induces neurological manifestations (3), whereas rare case reports argue a direct viral effect on the central nervous system (CNS) (4-7). However, only a few studies reported a detailed description of clinical manifestations and biological findings in the cerebrospinal fluid (CSF) in large cohorts (8-11), and a confrontation with neuroimaging findings has not been reported yet. This single-center study conducted in a well-characterized cohort of COVID-19 patients with neurological signs was designed to address this issue. The aim of this paper is to describe the neurological manifestations of 58 patients with regard to CSF analysis and neuroimaging findings.

Material and methods

Patient cohort

During COVID-19 outbreak, between March 1st and May 31st, 2020, 58 COVID-19 patients hospitalized at Strasbourg University hospitals were included. Inclusion criteria were: (i) confirmed SARS-CoV-2 infection by a positive RT-PCR assay on the nasopharyngeal swab or lower respiratory tract specimens; (ii) neurologic manifestations that lead to perform a lumbar puncture on the same day that a positive respiratory sample or within the following days; (iii) a test for SARS-CoV-2 RNA in the cerebrospinal fluid (CSF).

Clinical and laboratory data were retrieved from digital medical records according to the COVID-HUS study protocol (ClinicalTrials.gov identifier: NCT04405726).

This retrospective observational study was approved by the ethical committee of Strasbourg University Hospital.

CSF analysis

Cytological and biochemical analyses were collected retrospectively for all patients.

Elevation of white blood cells (WBC) count was defined as WBC count $> 5/\text{mm}^3$, hypoglycorrhachia as glycorrhachia $< 50\%$ of the concentration of blood glucose, and hyperproteinorachia as proteinorachia $> 0.45\text{g/L}$. The albumin quotient (CSF albumin/serum albumin) with age- corrected cutoffs was used to evaluate the blood- brain barrier (BBB) integrity. The Tibbling-Link IgG index $(\text{CSF IgG} \times \text{serum albumin}) / (\text{CSF albumin} \times \text{serum IgG})$ was used to assess an intrathecal synthesis of IgG (an index above 0.7 indicates a probable intrathecal synthesis of IgG), and oligoclonal band research was performed. An interleukin-6 (IL-6) level in CSF above 13 pg/mL was considered as high.

Virological assessment

SARS-CoV-2 identification was performed by RT-PCR testing of respiratory tracts (nasopharyngeal swab or lower respiratory specimens) and CSF according to current guidelines (Institut Pasteur, Paris, France; WHO technical guidance). The assay targets two regions of the viral *RNA-dependent RNA polymerase* (RdRp) gene, and the threshold limit of detection was 500 copies per mL. ELISA anti-SARS-CoV-2 IgG (Euroimmun, Lübeck, Germany) targeting the spike protein S1 domain was used in CSF for patients with CSF-specific IgG oligoclonal bands. Concomitant sera were also tested for SARS-CoV-2 IgG. The optical density of the samples and calibrators was detected at 450 nm. Cutoffs for IgG detection were calculated according to the manufacturer's instructions.

Brain MRIs protocols and interpretation

Imaging studies were conducted either on 1.5- or 3-Tesla MRI. The most frequent sequences performed were 3D T1-weighted spin-echo MRI with and without contrast enhancement, diffusion-weighted imaging, Susceptibility-weighted imaging, and 2D or 3D FLAIR before and after administration of gadolinium-based contrast agent. Brain MRIs were retrospectively reviewed by two neuroradiologists (S.K., and F.L. with 20 and 9 years of experience in neuroradiology, respectively) who reached a consensus concerning the final diagnosis.

Statistical analysis

Data were described using frequency and proportion for categorical variables, using mean and first and third quartiles for quantitative data. Categorical data were compared using Fisher exact test. Quantitative data were compared using Student's t-test or Wilcoxon test. A p-value lower than 0.05 was considered significant.

Data availability

We state that the data published are available and anonymized and will be shared upon request by email to the corresponding author from any qualified investigator for purposes of replicating procedures and results.

Results

Patient cohort (Table 1)

A total of 58 patients were included in this study. Patients were mostly men (38/58, 66%) with a median age of 62 years. The majority (47/58, 81%) of the patients were admitted to Intensive Care Units (ICU)s because of acute respiratory failure. The median between the onset symptoms of COVID-19, mostly respiratory, to lumbar puncture was 30 days.

Neurological manifestations (Table 1)

Neurological manifestations of the 58 patients included were varied: encephalopathy (confusion, impaired consciousness, pathological wakefulness when sedative therapies were stopped, agitation, hallucinations...) was frequent (81%) followed by signs of pyramidal tract dysfunction (16%) (such as muscle weakness, spasticity, hyperreflexia, and Babinski signs), seizures (10%) and headaches (5%). One patient (2%) presented with binocular diplopia (abducens nerve palsy), and another one with a static cerebellar syndrome (cerebellar ataxia). One patient (2%) with peripheral nervous system disorders related to Guillain-Barre acute polyneuritis should also be noted (Table 1). Encephalopathy were more frequent in ICU patients (41/47, 87% versus 6/11, 55%, $p=0.03$).

CSF analysis (Tables 2-3-4)

Ten (18%) patients have experienced an increase in the number of WBC. Detailed cell count was available for 7 of them: neutrophils predominance for four of them (one had bacterial meningitis) and lymphocytes predominance for the three others. Hypoglycorrhachia was present only in the patient with bacterial meningitis. Protein level and albumin level increase were found in 38% and 23%, respectively. A total of 40% of patients displayed an elevated albumin quotient suggesting an impaired BBB integrity. CSF-specific IgG oligoclonal band (type II) was found in five (11%) cases suggesting an intrathecal synthesis of IgG, and 26 (55%) patients presented identical oligoclonal band in serum and CSF (type IV). SARS-CoV-2 IgG antibodies were not detected in any CSF of the five

patients harboring CSF-specific IgG oligoclonal band, while concomitant sera were seropositive for all but one.

IL-6 level in CSF was available for 17 patients. All but one were admitted in an ICU unit, and 7 patients had IL-6 level above the cut-off.

Four (7%) patients presented a positive SARS-CoV-2 RT-PCR in CSF. One patient displayed viral load at $4.3 \log_{10}/\text{mL}$. For three others, the viral load was positive below the detection limit, which cannot rule out a blood contamination during the lumbar puncture. The four patients were admitted to ICU and presented with delirium. Three of them had an elevation of proteins level in CSF. A detailed description of these four cases is presented below.

No correlation was found between CSF findings, the place of hospitalization, and the major clinical and brain MRI findings.

Neuroimaging findings

Among the 58 patients included, 53 (91%) performed a brain MRI around the date of completion of the lumbar puncture (in addition to that, the case of Guillain-Barre also achieved a spinal cord MRI). Brain MRIs were considered normal, unrelated to the current acute event in 17 (32%) cases. Among the pathological brain MRIs (36; 68%), the neuroimaging findings were (figures 1,2):

- focal (single focus or multiple foci) leptomeningeal enhancement (LME) in 20 cases (38%), and one (2%) MRI showed multiple cranial nerve enhancement secondary to the Guillain-Barre syndrome.
- Acute cerebrovascular injuries, including extensive and isolated white matter microhemorrhages (12 cases, 23%), acute ischemic stroke (9 cases, 17%), and two (4%) patients with cerebral venous thrombosis.
- White matter lesions associating extensive, ill-defined, and confluent supratentorial white matter FLAIR hyperintensities (4 cases, 8%), acute inflammatory demyelinating lesions (2 cases, 4%), and FLAIR hyperintensities involving the middle cerebellar peduncles (1 patient, 2%).
- Grey matter lesions bringing together one (2%) patient with changes related to status epilepticus and another patient (2%) with FLAIR hyperintensities involving the mesial temporal lobe.

Patients could have had more than one pattern. Twenty-two patients were associated with one neuroimaging pattern, 11 with two patterns, and three showed three patterns.

As previously mentioned, encephalopathy was more frequent in ICU patients; this is not surprising since these are non-specific signs that could be found in many critically ill patients. By contrast, the other neurological manifestations described may point to possible focal brain injury.

Among the nine patients who presented pyramidal signs, five had LME, three had white matter microhemorrhages, two had acute ischemic strokes, one had extensive and confluent supratentorial white matter FLAIR hyperintensities, and for the last two patients, brain MRIs were considered normal.

Of the six patients with seizures, five performed a brain MRI, that was normal in two cases. In addition, one patient had cerebral venous thrombosis, one had extensive and confluent supratentorial FLAIR white matter hyperintensities; the last one had changes related to status epilepticus and FLAIR hyperintensities involving the mesial temporal lobe.

Of the three patients with headaches, two presented cerebral venous thrombosis, and the third brain MRI was normal.

Brain MRIs were normal for the two patients with an abducens nerve palsy or cerebellar ataxia.

Characteristics of the four patients tested positive for SARS-CoV-2 RNA in their CSF

Patient #1: was a 54-year-old male hospitalized in ICU for an ARDS. He received invasive mechanical ventilation and was placed in a prone position during three sessions. He received neuromuscular blockade for ten days. He showed a delayed awakening when the sedative drugs were stopped with no localizing central nervous system signs. An electroencephalogram was completed and was consistent with encephalopathy. An elevated WBC count ($7 \text{cells}/\text{mm}^3$) and CSF protein level

(0.52g/L) has been detected in the lumbar puncture, performed on day 27 of the onset of respiratory symptoms. Viral load measured on SARS-CoV-2 RT-PCR was positive at 4.3 log₁₀/mL in CSF and at 3.5 log₁₀/mL in respiratory tracts. Antineuronal antibodies were negative. Focal LME was described on brain MRI (figure 1), without other abnormalities. On day 50 of the onset of respiratory symptoms, he had been discharged from the ICU and remained in a hospital's conventional service. At this time, a dysexecutive syndrome was observed.

Patient #2: was a 67-year-old female hospitalized in ICU for an ARDS. She showed pathological wakefulness after prolonged sedation and bilateral corticospinal tract signs. Her SARS-CoV-2 viral load in respiratory tract was high at 8.3 log₁₀/mL. The lumbar puncture performed on day 23 of the onset of respiratory symptoms demonstrated a WBC count of 2cells/mm³, a CSF protein level of 0.23g/L, no increase in IgG level, Tibbling-link index, albumin level, or albumin quotient. An intrathecal synthesis of an oligoclonal band was found, as well as an increase in the IL-6 (300pg/mL) and TNF-α (68pg/mL) levels. SARS-CoV-2 RT-PCR in CSF was positive under the limit of detection. Brain MRI was considered normal.

Patient #3: was a 60-year-old female hospitalized in ICU for an ARDS. A few days after hospitalization, she was in a comatose state after resuscitation from cardiac arrest. The lumbar puncture performed on day 48 of the onset of respiratory symptoms demonstrated a WBC count of 1cell/mm³, an increase in CSF protein level (0.83g/L), in IgG level (102mg/L), and albumin quotient. The Tibbling-link index was not increased, and no monoclonal or oligoclonal bands were found. IL-6 (7pg/mL), interleukin-10 (0pg/mL), interferon-α (0pg/mL), and interferon-γ (2pg/mL) levels were not increased. SARS-CoV-2 RT-PCR in CSF and in respiratory samples were both positive under the limit of detection, as was viral load in respiratory samples. Focal LME was described on brain MRI.

Patient #4: was a 46-year-old male hospitalized in ICU for an ARDS. He presented persistently impaired consciousness after prolonged sedative therapies. The lumbar puncture performed on day 34 of the onset of respiratory symptoms demonstrated a WBC count of 0cell/mm³, an increase in CSF protein level (0.69g/L), in IgG level (61mg/L), and albumin quotient. The Tibbling-link index was not increased, and an oligoclonal band identical in CSF and serum was present. IL-6 (10pg/mL), interleukin-10 (0pg/mL), and TNF-α (0pg/mL) levels were not increased. SARS-CoV-2 RT-PCR in CSF and in respiratory samples were both positive under the limit of detection. Antineuronal antibodies were negative. Brain MRI was considered normal.

Discussion

To the best of our knowledge, this is the largest study to date, which describes neurological manifestations regarding CSF analysis and neuroimaging findings in COVID-19 patients.

In our cohort of 58 patients, we found four samples positive for SARS-CoV-2 in CSF. Among the three main studies (8-10) dedicated to CSF analysis, two slightly positive cases were described in a smaller series of 23 patients (10), but the hypothesis of contamination of the CSF by blood was raised. To date, rare case reports (4-7) have described positive CSF samples for SARS-CoV-2, and a few neuropathological studies (12-15) have detected its RNA in the brain (Table 5). Among our four patients positive for SARS-CoV-2 in CSF, three had a low viral load, which can also not rule out a blood contamination. On the other hand, the lumbar punctures were performed lately after SARS-CoV-2 infection at day 23, 34, and 48 after the onset of respiratory symptoms, respectively, and the median was 30 days in the entire cohort. This long delay could explain the negativity or the low positivity of our samples since the viral clearance is already significant at this time. Indeed, two of the three patients had a viral load below the limit of the detection in respiratory tracts at the time of lumbar puncture.

Brain MRI was normal for two of them, and the two others displayed focal LME, which were common findings during the COVID-19 outbreak (1,16).

CSF analyses showed normal or slightly increased WBC count (< 10/mm³) for most of our patients. Only three patients demonstrated substantial elevations in WBC count (one with bacterial meningitis

and two with acute ischemic stroke). WBC count elevation in CSF after ischemic stroke were previously reported (17).

CSF protein and albumin levels were increased in 38% and 23% of patients, respectively, which is concordant with previous reports (8,11).

The albumin quotient was increased in 40% of 47 tested patients, suggesting a BBB breakdown. This could be due to the cytokine release syndrome associated with severe COVID-19, which lead to BBB disruption (18-20). Among our eight patients associated with IL-6 or TNF α elevation in CSF, four (50%) had elevated albumin quotient.

A high level (55%) of identical oligoclonal bands in CSF and serum (type IV) were present in our study in agreement with previous reports (8,9). In this context, they were probably secondary to the systemic infection with passive diffusion into the CSF (21). Surprisingly, five of 47 (11%) tested patients demonstrated oligoclonal IgG bands restricted to CSF (type II). SARS-CoV-2 IgG antibodies were not detected in any CSF of these patients, while concomitant sera were seropositive for all but one. Nevertheless, the absence of detection of SARS-CoV-2 IgG antibodies in CSF of these patients could not rule out a presence of SARS-CoV-2 IgG antibodies. This could be due to a lack of sensitivity of the ELISA test and/or the fact that CSF was harvested late after the beginning of the infection. Four of them presented a normal brain MRI, and the last one demonstrated watershed cerebral infarction with focal LME. The other CNS infections having been eliminated by microbiological analyses, these specific oligoclonal bands may be a witness of parainfectious phenomena (21), corroborates by a description of focal LME in one patient (22). In the three main studies mentioned above, which described the characteristics of the CSF (8,9,11), only one patient was positive (type III) in the context of herpes simplex encephalitis (9). In addition to these five patients, two other cases showed an increase in the Tibbling-Link IgG index, i.e., the patient with bacterial meningitis (without oligoclonal IgG bands), and a patient with a type IV oligoclonal bands and focal LME on imaging. Even if this index is a reliable marker of intrathecal synthesis, it should be interpreted with caution when the test for specific oligoclonal bands is negative (23).

Concerning the neuroimaging findings, they can be separated into five main groups.

Focal LME, which were previously reported in COVID-19 patients (1,16, 24), were the most common pattern described. Among these 20 patients, two were positive for SARS-CoV-2 RNA in the CSF, and the hypothesis of viral meningitis due to the direct virus infiltration into the CSF should be raised, although the number of WBC was not really high (1 and 7cells/mm³). Alternative assumptions should also be discussed as they seem very relevant, such as disruption of the BBB secondary to cytokine release syndrome or para-infectious complications with immune-mediated processes triggered by SARS-CoV-2 (3, 16, 22, 25). This meningeal inflammation was also described in a recent neuropathological study that described a meningeal lymphocytic infiltrate in six patients (26). Extensive and isolated white matter microhemorrhages were present in 12 patients who were all admitted to the ICUs. This presentation can be invoked with the «critical illness-associated cerebral microbleeds» described in critically ill patients (27) and could be explained by hypoxemia with BBB disruption (5, 27-29).

Other commonly described findings were acute ischemic stroke (9 patients) and cerebral venous thrombosis (2 cases), as previously reported (16,24). This is not surprising since SARS-CoV-2 induced coagulopathy and is associated with increased prothrombotic events such as ischemic stroke and cerebral venous thrombosis. Of these nine patients, the majority (7/9) presented watershed cerebral infarctions, and all but one were admitted to ICUs. These patients have probably presented episodes of systemic hypotension during their hospitalization, promoting these ischemic complications. One other patient showed hypoxic-ischemic injuries after cardiac arrest. The last one was associated with small ischemic lesions, probably secondary to microembolism.

Four patients presented extensive and confluent supratentorial white matter FLAIR hyperintensities, in agreement with previous findings (5,24,28). Its precise pathophysiology remains unclear: viral encephalitis (not supported by CSF analysis) or postinfectious demyelinating diseases. Since three of them were admitted to ICUs for an ARDS, more general assumptions may be considered, such as delayed post-hypoxic leukoencephalopathy (30) and metabolic or toxic encephalopathy.

Two patients demonstrated acute inflammatory demyelinating lesions closed to what can be seen in case of acute disseminated encephalomyelitis (ADEM) or acute hemorrhagic leukoencephalitis, a

fulminant hemorrhagic form of ADEM. These last two diseases are considered autoimmune-mediated illnesses, and a few cases have been described in association with COVID-19 (31-33). A recent neuropathological study (34) described for the first time ADEM-like lesions in a patient with severe COVID-19 what reinforces this immunologic assumption. In addition, our series contains a case of Guillain-Barré, an example of post-infectious disease targeting the peripheral nervous system, as previously described in association with SARS-CoV-2 (35).

In conclusion, despite some limitations (low number of patients, missing data, and the study's retrospective design), our study improves the comprehension of the pathophysiology leading to neurological manifestations in COVID-19 patients. A direct viral involvement appears to be uncommon (viral isolation from CSF in four patients, three with a low viral load, and normal WBC count). A greater concern may be parainfectious or postinfectious immune-mediated disorders (specific oligoclonal IgG bands in five patients, increase in the Tibbling-Link IgG index in two other, and presence of LME, compatible, at least in part, with this hypothesis, acute inflammatory demyelinating lesions in two patient, and one patient with Guillain-Barre syndrome). Nevertheless, the main mechanisms of neurological damage probably involve systemic reactions such as cytokine release syndrome (elevated cytokines and albumin quotient in CSF), hypercoagulable state (cerebral venous thrombosis) or are secondary to the patient's critical condition (severe hypoxemia with disruption of the BBB, systemic hypotension with watershed infarcts).

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Abbreviations

ADEM: Acute disseminated encephalomyelitis

ARDS: Acute respiratory distress syndrome

BBB: Blood-brain barrier

CNS: Central nervous system

Ct: Cycle threshold

CSF: Cerebrospinal fluid

ICU: Intensive care unit

IgG: Immunoglobulin G

IL-6: Interleukin-6

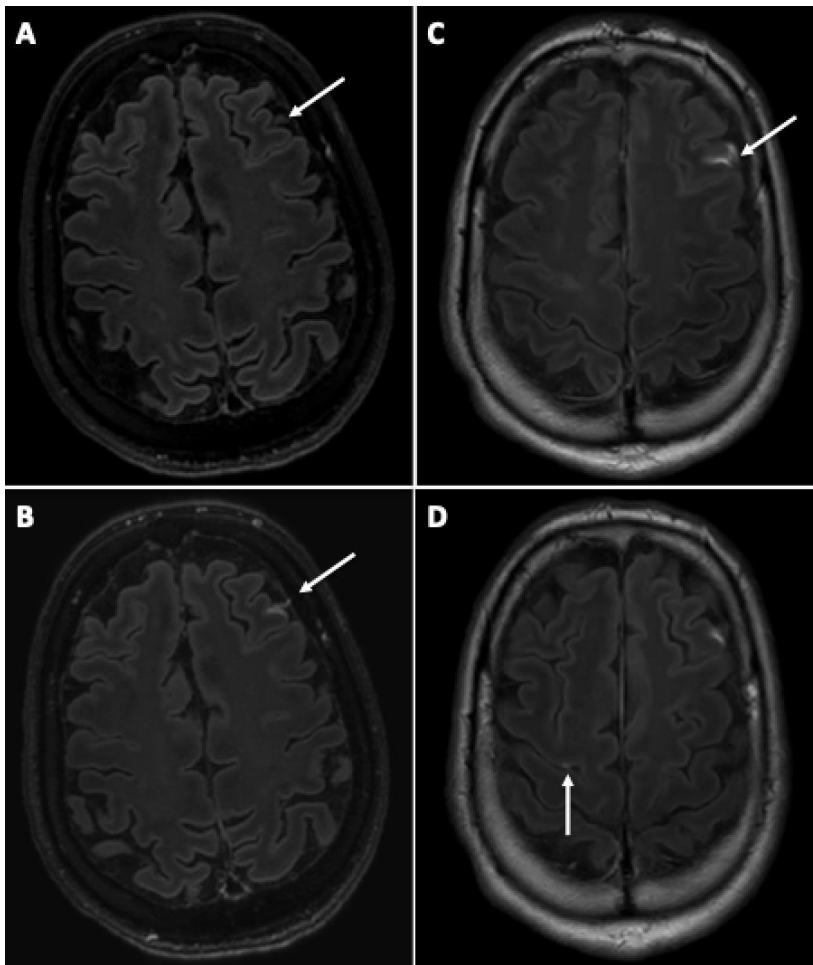
LME: Leptomeningeal enhancement

RT-PCR: Reverse transcriptase-polymerase chain reaction

WBC: White blood cells

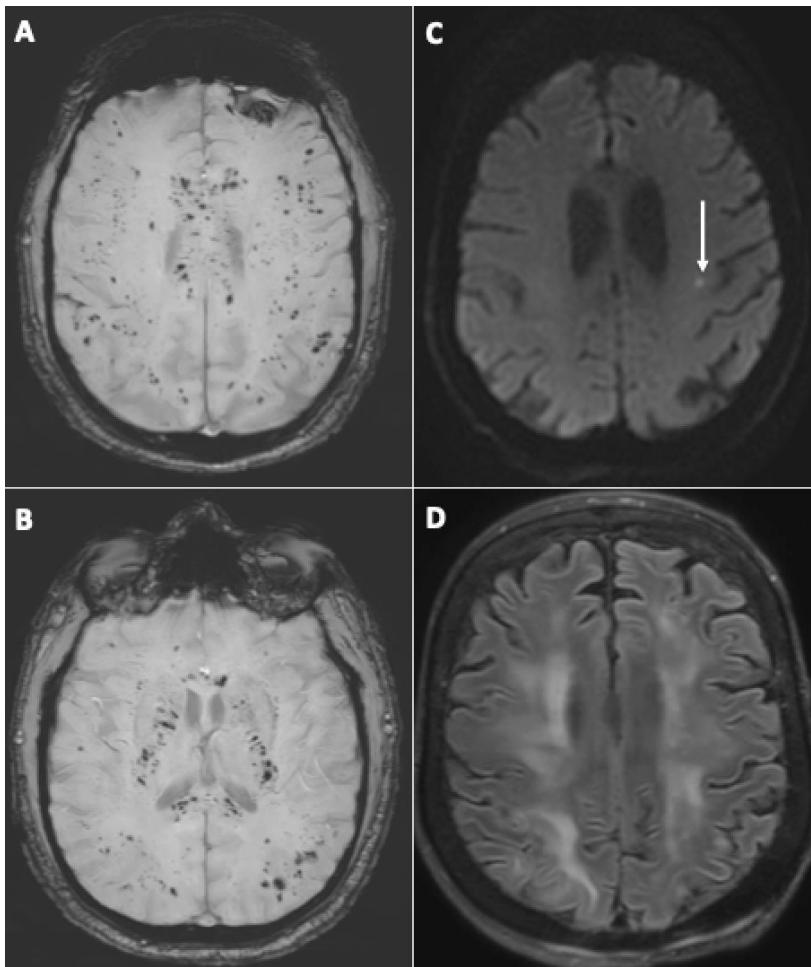
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Figure 1:



54-year old man (patient #1) tested positive for SARS-CoV-2 RNA in his CSF. Axial 3D FLAIR before (A) and after (B) contrast, axial delayed post-contrast FLAIR (C,D). Left frontal leptomeningeal linear FLAIR enhancement (B), not visible on pre-contrast FLAIR (A), but better seen on delayed after contrast FLAIR weighted MR images (C). Punctiform right precentral leptomeningeal enhancement (D).

Figure 2 :



Three other patients tested negative for SARS-CoV-2 RNA in their CSF. Axial susceptibility-weighted MR images (A, B), axial Diffusion (C), and axial FLAIR (D).

A, B : 57-year old man with white matter diffuse microhemorrhages appearing as multiple small hypointense foci within the corpus callosum, the internal capsules, and the juxtacortical white matter.

C: 81-year old woman with watershed cerebral infarction.

D: 71-year old woman with extensive and confluent supratentorial white matter FLAIR hyperintensities.

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Table 1: Epidemiologic profile and neurologic manifestations

	All patients (n=58)	No ICU admission (n=11)	ICU admission (n=47)	p-values
Sex (men)	38 (66%)	6 (55%)	32 (68%)	0.49
Age (years)	62 (55-70)	56 (47-69)	62 (57-70)	0.29
Time from onset of symptoms (most often respiratory) to lumbar puncture (days)	30 (18-36)	20 (17-30)	32 (19-37)	0.08
Neurologic manifestations				
<i>Encephalopathy</i>	47 (81%)	6 (55%)	41 (87%)	0.03
<i>Clinical signs of corticospinal tract involvement</i>	9 (16%)	0	9 (19%)	0.18
<i>Seizures</i>	6 (10%)	3 (27%)	3 (6%)	0.08
<i>Headaches</i>	3 (5%)	2 (18%)	1 (2%)	0.09
<i>Binocular diplopia</i>	1 (2%)	1 (9%)	0	1
<i>Cerebellar syndrome</i>	1 (2%)	0	1 (2%)	1
<i>Peripheral nervous system disorders related to Guillain-Barre acute polyneuritis</i>	1 (2%)	1 (9%)	0	1

Data are number and percentage or median with first and third quartile.

Table 2: Cerebrospinal fluid analysis and confrontation with type of hospitalization

CSF analysis	Normal range	All patients (n=58)	No ICU admission (n=11)	ICU admission (n=47)	p-value
WBC count (/mm³) (N=55)	< 5/mm ³	1 (0-3)	1 (0-3)	1 (0-3)	0.85
Elevated WBC count	-	10/55 (18%)	1/9 (11%)	9/46 (20%)	1
Hypoglycorrhachia (N=58)	> 50% of the concentration of blood glucose	1 (2%)	0	1 (2%)	1
Proteinorachia (g/L) (N=58)	0.15-0.45g/L	0.4 (0.29-0.58)	0.4 (0.29-0.6)	0.3 (0.22-0.57)	0.96
Protein elevation	-	22 (38%)	4 (36%)	18 (38%)	1
Albumin (mg/L) (N=47)	130-350 mg/L	188 (135-324)	180 (145-434)	188 (128-315)	0.93
Albumin elevation	-	11/47 (23%)	3/7 (43%)	8/40 (20%)	0.33
Albumin quotient elevation	Age related	19/47 (40%)	3/7 (43%)	16/40 (40%)	1
Immunoglobulin G (mg/L) (N=47)	10-34mg/L	33 (21-55)	34 (27-55)	33 (20-55)	0.21
Elevated IgG	-	21/47 (45%)	3/7 (43%)	18/40 (45%)	1
Tibblink-link IgG index elevation (N=47)	-	3/47 (6%)	0/7	3/40 (8%)	1
Oligoclonal IgG bands (OBs) (N=47)					
No OBs		16/47 (34%)	4/7 (57%)	12/40 (30%)	0.2
CSF-specific IgG OBS (type II)		5/47 (11%)	1/7 (14%)	4/40 (10%)	0.57
Identical OBs in serum and CSF (type IV)		26/47 (55%)	2/7 (29%)	24/40 (60%)	0.21
Positive RT-PCR for SARS-CoV-2 (N=58)	-	4/58 (7%)	0/11	4/47 (9%)	1
Interleukin-6 elevation (N=17)	(0-13pg/mL)	7/17 (41%)	0/1	7/16 (44%)	1
TNFα elevation (N=8)	(0-5pg/mL)	5/8 (63%)	N/A	5/8 (63%)	1

CSF analysis	Normal range	All patients (n=58)	No ICU admission (n=11)	ICU admission (n=47)	<i>p-value</i>
Presence of neuronal antibodies (N=26)	–	0/26	0/2	0/24	<i>1</i>

Data are number and percentage or median with first and third quartile.
N is the total number of patients with available data.

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Table 3: Cerebrospinal fluid analysis and confrontation with neuroimaging findings

	Brain MRI			LME*			WM MH**		
	Normal (n=17)	Abnormal (n=36)	<i>p-values</i>	Yes (n=20)	No (n=33)	<i>p-values</i>	Yes (n=12)	No (n=41)	<i>p-values</i>
WBC count (/mm ³) (N=50)	1 (0-3)	1 (0-4)	0.29	1 (0-2.5)	2 (0-3)	0.75	0 (0-3)	2 (1-3)	0.18
↑ WBC count	1/15 (7%)	8/35 (23%)	0.24	4/19 (21%)	5/31 (16%)	0.72	2/12 (17%)	7/38 (18%)	1
Proteinorachia (g/L) (N=53)	0.38 (0.29-0.45)	0.41 (0.3-0.65)	0.054	0.39 (0.29-0.6)	0.4 (0.3-0.6)	0.76	0.42 (0.3-0.5)	0.4 (0.3-0.6)	0.97
↑ Protein	5/17 (29%)	15/36 (42%)	0.54	8/20 (40%)	12/33 (36%)	1	4/12 (33%)	16/41 (39%)	1
Albumin (mg/L) (N=46)	167 (125-249)	188 (142-372)	0.18	188 (121-309)	190 (139-374)	0.83	188 (144-250)	188 (135-378)	0.65
↑ Albumin	2/15 (13%)	9/31 (29%)	0.29	3/17 (18%)	8/29 (28%)	0.5	1/11 (9%)	10/35 (29%)	0.25
↑ Albumin quotient	5/15 (33%)	13/31 (42%)	0.74	5/17 (29%)	13/29 (45%)	0.36	3/11 (27%)	15/35 (43%)	0.49
IgG (mg/L) (N=46)	33 (19-49)	33 (25-61)	0.13	32 (21-46)	34 (20-56)	0.47	26 (22-40)	37 (20-57)	0.35
↑ IgG	6/15 (40%)	15/31 (48%)	0.75	7/17 (41%)	14/29 (48%)	0.76	3/11 (27%)	18/35 (51%)	0.19
↑ Tibbling-link IgG index (N=46)	1/15 (7%)	2/31 (6%)	1	1/17 (6%)	2/29 (7%)	1	0/11 (0%)	3/35 (9%)	1
Oligoclonal IgG bands (OBs) (N=46)									
<i>No OBs</i>	4/15 (27%)	12/31 (39%)	0.51	5/17 (29%)	11/29 (38%)	0.74	4/11 (36%)	12/35 (34%)	1

<i>Type II</i>	4/15 (27%)	1/31 (3%)	0.03	1/17 (6%)	4/29 (14%)	0.63	0/11 (0%)	5/35 (14%)	0.31
<i>Type IV</i>	7/15 (47%)	18/31 (58%)	0.53	11/17(65%)	14/29 (48%)	0.36	7/11 (64%)	18/35 (51%)	0.51
Positive RT-PCR for SARS- CoV-2 (N=53)	2/17 (12%)	2/36 (6%)	0.58	2/20 (10%)	2/33 (6%)	0.63	0/12 (0%)	4/41 (10%)	0.56

*LME: leptomenigeal enhancement

**WM MH: white matter microhemorrhages

Data are number and percentage or median with first and third quartile

N is the total number of patients with available data.

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Table 4: Cerebrospinal fluid analysis according to main clinical findings

	Encephalopathy			Pyramidal signs		
	Yes (n=47)	No (n=11)	<i>p-values</i>	Yes (n=9)	No (n=49)	<i>p-values</i>
WBC count (/mm ³)	1 (0-3)	1 (0.4-1)	0.49	1.5 (0.8-2.3)	1 (0-3.5)	0.83
↑ WBC count (N=55)	9/46 (20%)	1/9 (11%)	1	0/8 (0%)	10/47 (21%)	0.33
Proteinorachia (g/L) (N=58)	0.4 (0.29-0.57)	0.32 (0.29-0.57)	0.9	0.3 (0.25-0.32)	0.4 (0.3-0.58)	0.08
↑ Protein	18/47 (38%)	4/11 (36%)	1	2/9 (22%)	20/49 (41%)	0.46
Albumin (mg/L) (N=47)	188 (122-315)	200 (162-444)	0.29	172 (118-239)	190 (142-349)	0.36
↑ Albumin	8/39 (21%)	3/8 (38%)	0.37	1/8 (13%)	10/39 (26%)	0.66
↑ Albumin quotient	16/39 (41%)	3/8 (38%)	1	3/8 (38%)	16/39 (41%)	1
IgG (mg/L) (N=47)	33 (21-54)	34 (28-55)	0.85	25 (14-72)	34 (25-53)	0.31
↑ IgG	18/39 (46%)	4/8 (50%)	1	3/8 (38%)	19/39 (49%)	0.71
↑ Tibbling-link IgG index (N=47)	3/39 (8%)	0/8 (0%)	1	0/8 (0%)	3/39 (8%)	1
Oligoclonal IgG bands (OBs) (N=47)			1			0.87
<i>No OBs</i>	13/39 (33%)	3/8 (38%)		2/8 (25%)	14/39 (36%)	
<i>Type II</i>	4/39 (10%)	1/8 (13%)		1/8 (13%)	4/39 (10%)	
<i>Type IV</i>	22/39 (56%)	4/8 (50%)		5/8 (63%)	21/39 (54%)	
Positive RT-PCR for SARS-CoV-2 (N=58)	4/47 (9%)	0/11 (0%)	1	1/9 (11%)	3/49 (6%)	0.5

Data are number and percentage or median with first and third quartile
N is the total number of patients with available data

Table 5: Review of neuropathological studies with cerebral detection of SARS-CoV-2, or studies with positive analysis for SARS-CoV-2 in CSF

Author	Study area	Kind of study	Number of cases	Main results
Deigendesch (12)	Basel, Switzerland	Neuropathological	7 patients	4 patients with detection of SARS-CoV-2 RNA in olfactory bulbs
Hanley (13)	London, United Kingdom	Neuropathological	5 patients	1 patient with detection of SARS-CoV-2 RNA in brain
Rommelink (14)	Brussels, Belgium	Neuropathological	11 patients	9 patients with detection of SARS-CoV-2 RNA in brain
Solomon (15)	Boston, USA	Neuropathological	18 patients	5 patients with detection of SARS-CoV-2 RNA in brain
Destras (10)	Lyon, France	Virological	23 CSF samples	2 samples slightly positive for SARS-CoV-2 (contamination by blood?)
Moriguchi (4)	Yamanashi, Japan	Case report	1	Detection of SARS-CoV-2 RNA in CSF of 1 patient with brain MRI changes (FLAIR hyperintensities in the right mesial temporal lobe)
Kremer (5)	France (multicentric)	Radiological	37	Detection of SARS-CoV-2 RNA in CSF of 1 patient with brain MRI changes (FLAIR hyperintensities in the left mesial temporal lobe)
Fadakar (6)	Shiraz, Iran	Case report	1	Detection of SARS-CoV-2 RNA in CSF of 1 patient with brain MRI changes (acute cerebellitis)
Virhammar (7)	Uppsala, Sweden	Case report	1	Detection of SARS-CoV-2 RNA in CSF of 1 patient with brain MRI changes (acute necrotizing encephalopathy)

ICU: Intensive care unit