Central Nervous System Disorders in Severe SARS-CoV-2 Infection: detailed clinical work-up of eight cases

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Abstract

Objective

Case series with different clinical presentations indicating central nervous system (CNS) involvement in coronavirus disease 2019 (COVID-19) have been published. Comprehensive work-ups including clinical characteristics, laboratory, electroencephalography (EEG), neuroimaging and cerebrospinal fluid (CSF) findings are needed to understand the mechanisms.

Design

We evaluated 32 consecutive patients with severe SARS-CoV-2 infection treated at a tertiary care centre from March 09 to April 03, 2020 for concomitant severe central nervous system (CNS) symptoms occurring during their critical disease state. Those with CNS disorders were examined in detail regarding clinical characteristics and undergoing additional examinations, e.g. computed tomography (CT), magnetic resonance imaging (MRI), (EEG), (CSF) analysis and autopsy if they had died.

Results

Of 32 critically ill patients with COVID-19 eight (18%) had severe CNS involvement (mean [SD] age, 67.6 [6.8] years; seven men; two patients died). All eight patients had cardiovascular risk factors, most frequently arterial hypertension. Two patients presented with lacunar ischemic stroke and one with status epilepticus in the early phase. As most common presentation, six patients presented with prolonged impaired consciousness after termination of analgosedation. In all but one with delayed wake-up, neuroimaging or autopsy showed multiple cerebral microbleeds, in three of them with additional subarachnoid haemorrhage and in another two with additional small ischemic lesions. In three patients intracranial vessel wall sequence MRI was performed, for the first time to our knowledge. All cases showed contrast-enhancement of vessel walls in large and middle-sized cerebral arteries, suggesting vascular wall pathologies with an inflammatory component. CSF analysis showed normal cells counts and chemistry. RT-PCRs for SARS-CoV-2 in CSF were all negative, and no intrathecal SARS-CoV-2 specific IgG synthesis was detectable.

Conclusions

CNS disorders are common in patients with severe COVID-19. Different mechanisms might be involved. Besides unspecific encephalopathy and encephalitic syndromes, large vessel strokes might occur early after disease onset. In a later phase, microbleeds and microinfarctions indicate potential CNS small vessel disease. MRI vessel wall contrast enhancement suggests cerebral vascular wall pathologies with an inflammatory component. CNS disorders associated with COVID-19 may lead to long-term disabilities aggravating socio-economic damage. The mechanisms have to be investigated urgently in order to develop preventive and therapeutic neuroprotective strategies.

Introduction

Neurologic disorders in COVID–19 have been reported in 36.4% of the patients of the Wuhan series (1). Recently, more and more individual case descriptions with central nervous system (CNS) involvement have been published in Asia, Europe and North America (2–11).

Comprehensive workups of as many cases as possible are needed to understand a potential “Neuro-COVID–19” disease and, in a next step, to develop preventive as well as therapeutic strategies.

Below eight cases of critically ill patients with the primary diagnosis of severe COVID–19 pneumonia and subsequent neurologic complications examined with electroencephalography (EEG), neuroimaging and cerebrospinal fluid (CSF) analysis are presented. The findings are assigned to previously published case reports.

Methods

Study Design and Participants

We retrospectively analysed consecutive patients with severe COVID–19 treated at the Institute of Intensive Care Medicine, University Hospital Zurich from March 09, 2020 to April 03, 2020. The patients were evaluated for concomitant severe central nervous system (CNS) symptoms occurring during their critical disease state. Furthermore, the Institute of Intensive Care Medicine of the University Hospital Zurich supported the Graubuenden Cantonal Hospital by the means of consultative treatment regarding an additional critically ill COVID–19 patient with CNS symptoms who had been admitted there in the same time period. This case is also included in the study. The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee (ID 2020–00894). Written consent was given by the legal representatives as all patients were still incapable of judgment at hospital discharge.

Data Collection

Severe cerebral disorders triggering the additional examinations such as cranial computed tomography (CT) or magnetic resonance imaging (MRI), EEG as well as CSF analysis were: impaired consciousness (negative or delayed wake-up attempt after termination of analgosedation with persistent coma, stupor or delirium), acute cerebrovascular disease, clinical seizure / status epilepticus and myoclonic movements. At time of neurological assessment, midazolam serum levels were below the detection limit in all patients. SARS-CoV–2 infection was confirmed by reverse-transcription polymerase chain reaction assay (RT-PCR) in throat and or tracheobronchial samples (according to (12) or by Roche Cobas SARS-CoV–2 test). Metagenomic virus sequencing was performed as described (13). All examinations (laboratory values, chest radiographs and CTs) as well as neuroimaging, EEG and CSF analysis were performed according to the clinical needs of the patients. Electronic medical records were reviewed for date of COVID–19 symptom onset, neurological symptom onset, age, sex, pre-existing medical conditions (arterial hypertension, diabetes, smoking, cardiac disease, cerebrovascular disease, immunosuppression because of malignancy or immunosuppressive treatment, lung disease, treatment with ACE inhibitors or angiotensin II receptor antagonists, statins, anticoagulants) and specific initial symptoms, especially anosmia/hyposmia, neuropsychiatric symptoms and focal neurologic deficits. Data on empiric COVID–19 therapies (Hydroxychloroquine, Remdesivir) and pre-intubation worst oxygen saturation (SpO_2) were recorded. In addition to daily routine laboratory tests (blood cell counts, chemistry, coagulation testing) in patients with neurological deficits, serum was analysed for glucose, lactate, immunoglobulins indices, interleukin–6, antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), antibody to native DNA (nDNA), lupus anticoagulant, anti-cardiolipin, anti-β2-glycoprotein I, anti-SSA/Ro, anti-SSB/La and anti-IgLON5 antibodies. Patient serum was tested for antibodies for viral infections (including SARS-CoV–2, herpes simplex virus (HSV), varizella zoster virus (VZV), cytomegaly virus (CMV), hepatitis B virus (HBV) and human immunodeficiency virus (HIV)). Laboratory values on the day of CSF sampling or the day before were analysed. CSF samples were analysed for cell count (white and red cells) and cell composition, chemistry (glucose, lactate and protein), bacterial culture, neurotropic viruses using RT-PCR to detect HSV, VZV, CMV and SARS-CoV–2 and immunology parameters including oligoclonal bands, total CSF/serum IgG-, IgA- and IgM quotients as well as SARS-CoV–2-, HSV1-, CMV-, VZV-specific and anti-IgLON5 antibodies. SARS-CoV–2 antibodies in serum and CSF were tested using an in-house developed, bead-based antibody assay using Luminex that detects IgG, IgA and IgM antibodies against subunit 1 (S1) and subunit 2 (S2) of the spike protein and nucleoprotein (NP) of SARS-CoV–2. Mean fluorescence intensity (MFI) was assessed using FLEXMAP 3D (Luminex). Antibody reactivity was assessed in arbitrary units (AU) using a standard curve obtained from a serial dilution of the respective standard serum for interpolating MFIs by four parameter logistic curve fit. AUs within the linear part of the standard curve were multiplied by the corresponding dilution factor to obtain absolute AU. To calculate intrathecal SARS-CoV–2-, HSV1-, CMV-, and VZV-specific IgG synthesis, the antigen-specific CSF/serum antibody index (CAI_{spec}) was calculated according to (14).

We recorded 20 minutes EEGs using standard 25 channel montage (10/20). Electrophysiological analysis included visual scoring for epileptic activity, vigilance, background activity, focal slowing and quantitative spectral analysis. We performed standardized painful and acoustic stimuli to test for EEG reactivity in all patients.

CT neuroimaging was performed on a various scanner systems: SOMATOM Force, X.cite, Definition, and Edge plus, Siemens Healthineers, Forchheim, Germany. MRI was performed on 3.0 Tesla scanners (either Ingenia; Philips, Eindhoven, The Netherlands, or Skyra, Siemens Healthineers, Forchheim, Germany). The standard imaging protocol included axial T2-weighted (w), diffusion-weighted images (DWI) with b1000 m s/mm2, apparent diffusion coefficient (ADC) map images, and susceptibility weighted imaging (SWI) sequences. Furthermore, 3D T1-weighted (non-contrast and contrast enhanced) as well as 3D fluid attenuated inversion recovery (FLARI) sequences were acquired, each with axial, coronal and sagittal reconstructions. Intracranial MRI vessel wall imaging was performed in three patients using high resolution T1w dark blood non-contrast and contrast enhanced space sequences (Skyra, Siemens Healthineers, Forchheim, Germany).

Statistical Analysis

Descriptive statistics and frequency analysis are calculated to describe characteristics of the study sample and overall prevalence of concomitant factors. Mean and standard deviation (SD) are used for normally distributed data and median and range for data that were not normally distributed. Categorical variables are expressed as counts and percentages. The time from onset of the first symptoms of COVID–19 to manifestation of CNS symptoms was calculated in days.

Results

Demographic and Clinical Characteristics

Among 32 critically ill patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV–2) infection eight patients (18%) presented with severe CNS involvement. Their mean (SD) age was 67.6 (6.8) years, seven were male. Two patients died due to respiratory or multiorgan failure. Baseline characteristics are given in Table 1. All patients had cardiovascular risk factors, most frequently hypertension as a pre-existing condition. The characteristics of the patients during the course of the disease are given in Table 2. All patients were treated with invasive mechanical ventilation and all but one with prone positioning. Seven had to be treated with continuous renal replacement therapy due to renal failure. Three patients suffered from myocardial injury characterized by elevated troponin, myoglobin and creatinine phosphokinase (patients 1,2 and 6) and one from acute mesenteric ischemia requiring surgery and leading to multiorgan failure (patient 1).

Clinical and Neuroradiological Characteristics

CNS symptoms became manifest on day 17.5 in median (range day 2 to 34). In no patient anosmia/hyposmia or neuropsychiatric symptoms could be revealed in the medical history. In two patients (patients 6 and 7), CNS symptoms included primary focal neurological deficits due to an ischemic stroke, in one of them manifesting before pneumonia became evident (patient 7). In both patients single lacunar ischemic lesions corresponding to their primary focal neurological deficits were present in the initial CT. Their follow-up MRI scans showed additional small ischemic lesions in different vascular territories. All but one patient (patients 1, 2, 4, 5, 6, 7 and 8) presented with impaired consciousness for several days after termination of analgosedation. In all but two patients (patients 3 and 4), CT or MRI scans performed later in the course of the disease, showed multiple cerebral microbleeds, in three of them with additional subarachnoid haemorrhage (patients 1, 2 and 8) (Figure 1). Three patients were examined with intracranial vessel wall sequence MRI (patients 2, 6 and 7). In all three patients vessel wall contrast enhancement of large to middle-sized cerebral arteries was found (Figure 2).

One patient was admitted from a peripheral hospital due to status epilepticus (patient 3) which was successfully treated with levetiracetam and valproate. Thereupon pronounced myoclonic movement patterns occurred on all extremities. Except generalized brain atrophy, CT and MRI scans showed no abnormal findings.

Laboratory Findings

Laboratory findings are given in table 3. At time of CNS symptoms the median values for lymphocyte count were 1.84 x 10^9G/L (range 1.03 to 2.47 109 G/L), CRP 87 mg/L (range 8 to 240 mg/L), IL–6 48.5 ng/L (range 6.4 to 594 ng/L), fibrinogen 5.8 g/L (range from 4.5 to 8.1 g/L) and D-dimer 6.45 mg/L (range from 2.6 to 20 mg/L).Autoantibodies such as ANA, ANCA, anti-dsDNA, anti-cardiolipin, anti- β2-glycoprotein as well as lupus anticoagulant were negative in patient 5 and 7, in patient 6 only the unspecific IgA antibodies for anti-cardiolipin and, anti-β2-glycoprotein, as well as and ANA were slightly elevated.

CSF could be analysed in seven patients. 2 days (range 0—31) after first observation of CNS symptoms after analgosedation and 17.5 days (range 2—34) after onset of COVID–19 pneumonia. Cell counts as well as chemistry (except slightly elevated proteins in patients 3 and 5) were normal in all patients. All CSF samples probed negative for SARS-CoV–2 and other neurotropic viruses. While SARS-CoV–2 IgG was present in serum of all patients, no intrathecal SARS-CoV–2 IgG synthesis was detectable. In two patients (patients 3, 7 and 8) metagenomic virus sequencing from CSF resulted in negative findings.

EEG Findings

All patients showed similar, yet unspecific EEG patterns with severe to moderate background slowing and anterior rhythmic delta activity consistent with metabolic encephalopathy. No interictal epileptiform discharges were found. However, we found stimulus induced periodic discharges (patient 5) and rhythmic frontal theta activity in myoclonic status (patient 2) as a correlate for enhanced epileptogenicity.

Autopsy Findings

Brain autopsy of one patient (patient 1) showed acute microbleeds in the pontine tegmentum and acute microinfarcts in the basal ganglia. Around the rostral surface of the cerebellum an extensive, acute subarachnoidal haemorrhage was seen. Adjacent cerebral tissue showed multiple fresh, partially confluent, microinfarcts and parenchymal haemorrhages. In addition, fresh blood was found in the perihippocampal area.

Outcome

At time of submission all six surviving patients were still hospitalized but showed significant neurological recovery (three with still mild cognitive deficits, two with slight to moderate tetraparesis indicating critical illness neuro- and myopathy, one with persistent myoclonic movements). The two stroke patients showed no focal neurological deficits anymore.

Discussion

In the Wuhan series, 27 of 88 patients hospitalized with severe COVID–19 infection (30.7%) had CNS symptoms (1). 13 of them (48.1%) suffered from impaired consciousness, five from acute cerebrovascular disease (18.5%), one from ataxia and one from seizure. Neurological features were found in 58 of 64 consecutive hospitalized patients in Strasbourg (4). Most of them occurred when sedation was withheld (67%) and consisted of agitation (69%), confusion (65%) and diffuse corticospinal tract signs (67%).

In the present patient population of 32 ICU patients with COVID–19, eight (25%) had severe CNS symptoms, among them two with hemiparesis and lacunar ischemic stroke and one with status epilepticus in the early phase. As most common presentation, six patients presented with prolonged impaired consciousness after termination of analgosedation, three with temporarily delirious state.

The different patterns of our cases suggest that variable pathogenesis may lead to CNS disorders in COVID–19. Evaluating and summarizing the published small series and individual cases (1–3, 5–11), neurologic sequelae can be assigned to the following pathophysiological groups:

Unspecific, related to severity of disease

In one case hypoxic encephalopathy, presenting as status epilepticus and myoclonic movements, and in another case, metabolic-toxic encephalopathy, associated with uraemia, might be unspecific cerebral complications in two of our critically ill COVID–19 patients. In both patients neuroimaging showed no specific findings but frontotemporal brain atrophy, which might be associated with sepsis-induced brain dysfunction (15). Sepsis-associated encephalopathy, which typically presents as confusion and coma, is reported in up to 70% of patients with sepsis (16). All our patients' EEG examinations showed severe generalized background slowing, indicating global cognitive dysfunction and occurring in patients after recovery from severe sepsis (17). In the Beijing series, critically ill COVID–19 patients developing septic shock and multiorgan failure have been described (18). In 76% of the cases cultures for bacteria and fungus were negative. The authors, therefore, used the term "viral sepsis". As in sepsis induced by other microorganisms, hyperactivation of proinflammatory cytokines and chemokines play an important role in severe COVID–19 and may be associated with septic encephalopathy. Finally, epileptic activity seems to occur only rarely in COVID–19 patients (0.5% in the Wuhan series) (1) and might be related to hypoxia, multiorgan failure, and metabolic disorder rather than to CNS infection (19). In agreement, also in our series the occurrence of epileptic activity and myoclonic status in patient 3 was most probably caused by hypoxic brain injury.

Large and small cerebral vessel disease

Two of our patients presented with acute ischemic stroke in the early phase of their disease. A series of five cases of large -vessel stroke in patients younger than 50 years has been described in New York City (6). In the Wuhan series, the incidence of stroke in hospitalized patients was about 5% (1). Severe infections, especially respiratory-related, are known to trigger acute cerebrovascular events (20). Severe COVID–19 mostly develops in patients with cardiovascular risk factors and is characterized by a pronounced proinflammatory early phase (18), both factors even aggravating the risk for stroke at disease onset. In Strasbourg, 23 patients with neurological symptoms were examined with MR imaging (4). Three asymptomatic patients had small ischemic strokes and bilateral frontotemporal hypoperfusion was noted in all 11 patients who underwent perfusion imaging (4). Contrast -enhanced perfusion MR was not performed in our series. However, the unspecific EEG patterns in our patients with background slowing and occasional anterior rhythmic delta activity, consistent with unspecific encephalopathy, might also reflect frontal hypoperfusion.

Further extraordinary findings in our series were detected later in the course of the disease. In all but one patient with delayed wake-up, neuroimaging or autopsy showed multiple cerebral microbleeds, in three of them with additional subarachnoid haemorrhage and in another two with additional small ischemic lesions, indicating CNS small vessel disease. Different factors might explain the involvement of small cerebral vessels. All patients had cardiovascular risk factors, most of them hypertension. The distribution of the microbleeds, however, was typical for hypertension in only one patient. None of our patients had a history of cerebral amyloid angiopathy. As in other series, all our patients had a hypercoagulable state with increased fibrinogen and D-dimer levels (11, 21), which might lead to thrombosis of small cerebral vessels. Only one patient, however, fulfilled the criteria of disseminated intravascular coagulation disorder (> 5 points according to the International Society on Thrombosis and Haemostasis criteria) (22), which is known to be associated with acute cerebral micro-angiopathy. Immune-mediated and infectious vasculitis may cause CNS small vessel disease (23) and a certain type of vasculitis involving cerebral vessels might be induced by COVID–19 as well.

In three patients with severe COVID–19 intracranial vessel wall sequence MRI scans were performed, for the first time to our knowledge. MR vessel wall imaging showed contrast -enhancement of vessel walls in large and middle-sized cerebral arteries, suggesting vascular wall pathologies with an inflammatory component. However, MRI vessel wall contrast- enhancement is not specific for vasculitis involving cerebral vessels. None of our patients showed inflammatory signs in the CSF or characteristic autoantibodies indicating systemic vasculitis. Chen et al. found vessel wall contrast -enhancement in 45.8% of the patients with reversible cerebral vasoconstriction syndrome (RCVS) (24). The authors suggest that, among other factors, endothelial dysfunction might contribute to vascular wall inflammation in RCVS. However, none of our patients had typical signs of RCVS such as thunderclap headache and/or reversible multifocal cerebral vasoconstrictions.

Contrast -enhancement of vessel walls as well as the pattern of micro-bleedings and multiple small infarctions indicate that large, middle-sized as well as small cerebral vessels are involved. An autopsy study in patients with severe COVID–19 revealed vascular involvement in multiple organs (25). Lymphocytic endotheliitis was found in lung, heart, kidney, liver and small intestine. Furthermore, viral inclusion structures, could be found in endothelial cells. The angiotensin-converting enzyme 2 (ACE2), as the main host cell receptor of SARS-CoV–2 (26), albeit at lower concentrations, is also expressed in the endothelium and vascular smooth muscle cells of the brain (27). It might be hypothesized that the endothelium of brain vessels might be directly affected by the virus or that the virus induces a parainfectious immune-mediated inflammation of the endothelium. However, we did not find any inflammatory CSF syndrome as a sign of infectious cerebral vasculitis in our patients or signs of perivascular inflammatory cell infiltration in the one post-mortem analysis performed. Another mechanism might be, that the cerebral vessels might be affected by the inflammatory state in the peripheral blood. Prolonged increased levels of IL–6, IL–10, IL–2 and IFN γ have been described in severe cases and may play an important role in the immunopathology of COVID–19 (28). In our patients, serum IL–6 was elevated in all but one patient up to levels of 594 ng/L. However, in all of them IL–6 values in the serum were higher than in CSF, which contradicts its intrathecal synthesis. Still, these observations do not

exclude the possibility of damage to cerebral vessels induced by the hyperinflammatory state in the peripheral blood. Cytokines or inflammation-induced metabolic changes leaking from peripheral blood to the CNS micromilieu might lead to disseminated focal disturbances of the blood brain barrier and dysfunction of the respective surrounding brain tissue.

Encephalitis

Singles cases with COVID–19 and meningo-encephalitis, one case with acute necrotizing encephalopathy and one with acute disseminated encephalomyelitis (ADEM) have been described (2, 3, 5, 7–11). Neuroinvasion is hypothesized to occur via hematogenous or neuronal route as over the olfactory nerve (29). In two cases with neuropsychological symptoms, one of them with status epilepticus, lymphocytic pleocytosis but negative RT-PCR for SARS-CoV–2 was found in the CSF (2). In another case suffering from disorientation and hallucinations, CSF analysis also revealed lymphocytosis (3). To our knowledge, up to date, gene sequencing confirmed the presence of SARS-CoV–2 in the CSF in Beijing in only one case (30) and RT-PCR was positive in only one patient in Japan (5). None of our patients, not even those with status epilepticus, showed inflammatory signs neither in neuroimaging nor in the CSF. RT-PCR for SARS-CoV–2 in the CSF was negative in all patients. Intrathecal IgG production against the SARS-CoV–2 could not be demonstrated and even metagenomic virus sequencing was negative in two patients. Therefore, neither direct neuroinvasive potential nor directly CNS-directed parainfectious injury could be demonstrated in our patients.

Limitations

Only eight patients were studied. All were severely ill, entering the ICU with respiratory failure. Mild neurological symptoms at disease onset as headache, dizziness and taste or smell impairment could no longer be reliably evaluated. Furthermore, CNS symptoms might have remained undetected in patients who were under analgosedation. Diagnostics with neuroimaging and CSF analysis might not have been performed at the time of the occurrence of cerebral complications. Therefore, inflammatory signs in the CSF, might have been missed. Furthermore, RT-PCR tests for SARS-CoV–2 in the CSF are not yet sufficiently clinically validated regarding sensitivity and timing of lumbar puncture after onset of symptoms. We cannot exclude the possibilities of (i) transient SARS-CoV–2 RT-PCR positivity in the CSF through true invasion of CNS with SARS-CoV–2, which turned out to be negative at the time of lumbar puncture, or (ii) concentrations of SARS-CoV–2 in the CSF below detection limit of our RT-PCR assay. Additional search for intrathecal SARS-CoV–2-specific IgG production as a sign of humoral immune reaction against viral infection of CSF space turned out negative. In other viral CNS infections such as herpes encephalitis or tick-borne encephalitis, intrathecal antiviral IgG production usually consistently occurs 10–14 days after onset of symptoms, but may occur occasionally as early as 3 days after disease onset (31–33). Our observation of no intrathecal SARS-CoV–2 IgG production may be explained by the possibilities, that SARS-CoV–2 never entered CNS and therefore no intrathecal immune response was mounted or because intrathecal SARS-CoV–2-specific IgG synthesis occurred after lumbar puncture. In analogy to other human viral CNS infections, the consistent combination of negative SARS-CoV–2 RT-PCR and absence of intrathecal SARS-CoV–2 IgG production 2 days (range 0—31) after onset of CNS disorder argues relatively against a direct invasion of CNS by SARS-CoV–2, but we cannot exclude the possibility of a differential diagnostic window, which might have been missed.

Conclusions

Severe CNS disorders are common in patients with severe COVID–19 and different pathomechanisms might be involved. Besides unspecific encephalopathic patterns and encephalitic syndromes described as case reports, large vessel strokes might occur more often early after disease onset. In a later phase, microbleeds and microinfarctions as well as vessel wall contrast enhancement occur, indicating large and small cerebral vessels to be involved. Patients with endothelial dysfunction due to cardiovascular risk factors, mostly hypertension, might be especially at risk. Whether SARS-CoV–2 directly affects endothelial cells of brain vessels has to be investigated in basic research and more clinical cases. CNS disorders associated with COVID–19 can lead to long-term disabilities and may aggravate socio-economic damage. The mechanisms have to be investigated urgently in order to develop preventive and therapeutic neuroprotective strategies.

Declarations

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Tables

Table 1: Baseline Characteristics of Patients with CNS manifestations

Characteristics	No.
Mean age, years (SD)	67.6 (6.8)
Sex	
Female	1
Male	7
Pre-existing comorbidities	
Arterial hypertension	7
Diabetes	6
Smoking	0
Obesity	2
Hypercholesterolemia	1
Cardiac disease	1
Cerebrovascular disease	1
Immunosuppressed state	1
Lung disease	1
Others	1
Pre-existing medication	
ACE-Inhibitors or angiotensin -II -receptor antagonists	4
Statins	2
Initial presentation	
Pneumonia	8
Ischemic stroke	1
CNS manifestation	
Delayed wake-up	7
Ischemic stroke	2
Status epilepticus	1
Myoclonic movements	2
Pupil disturbances	2

Abbreviations: CNS, central nervous system

Table 2: Characteristics of Patients with CNS disorders in the Course of the Disease

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age, y	58	68	66	81	65	66	75	62
Sex	Female	Male	Male	Male	Male	Male	Male	Male
Cardiovascular risk factors	Hypertension, diabetes, obesity	Hypertension, diabetes	Hypertension	Hypertension, diabetes	Hypertension	Hypertension, diabetes	Hypertension, diabetes, obesity	Dyslipidemia
Pre-existing disease; medication	Rosuvastatin, Torasemid, Metoprolol, Amlodipin, Valsartan, Gliclazid	None	Candesartan	Asthma; Lisinopril, Aspirin, Metformin, Insulin	Ocular myasthenia; Prednisolone, Mestinone, Valsartane, Amlodipine	Amlodipine, Metformin	Sick sinus syndrome, chronic venous insufficiency	Rosuvastatin
Empiric COVID-19 treatment	Hydroxychloro-quine	Hydroxychloro-quine	None	Hydroxychloro-quine	None	None	Hydroxychloro-quine	Hydroxychloro-quine
Pre-intubation/ worst SPO_2, %	68	89	Cyanosis at emergency intubation	83	86	93	85	90
Anticoagulation last 3 days before CNS disorder	Therapeutic anticoagulation with unfractionated heparin	Therapeutic anticoagulation with unfractionated heparin	Prophylactic dose of unfractionated heparin	Therapeutic anticoagulation with unfractionated heparin, Argotraban	Therapeutic anticoagulation with unfractionated heparin	Prophylactic dose of unfractionated heparin	Therapeutic anticoagulation with unfractionated heparin	High-prophylactic dose of unfractionated heparin
CNS disorder	Negative wake-up, non-reactive pupils after CPR	Delayed wake-up, myoclonic movements, later delirium	Status epilepticus, myoclonic movements	Negative wake-up, pathological breathing pattern	Delayed wake-up	Acute left ischemic stroke (right hemiparesis dysarthria), delayed wake-up	Acute left ischemic stroke (dysarthria, right facial palsy, right hemiparesis), delayed wake-up	Delayed wake-up, anisocoria
Concomitant condition*	IMV, prone positioning CRRT, mesenteric ischemia, myocardial injury	IMV, prone positioning CRRT, myocardial injury	IMV	IMV, prone positioning CRRT, HIT, uraemia, femoral vein thrombosis	IMV, prone positioning CRRT, jugular vein thrombosis, myocardial injury	IMV, prone positioning CRRT, ECMO, myocardial injury	IMV, prone positioning, CRRT	IMV, prone positioning, CRRT
Time from disease onset to first CNS symptoms	17	25	16	18	34	2 (primary diagnosis stroke)	17	22
Neuroimaging	CT: acute bilateral cerebellar subarachnoid haemorrhage	CT: acute subarachnoid haemorrhage right frontal lobe, focal brain swelling MRI: minor subarachnoid haemorrhage on various bilateral locations. MRI (VWI): vessel wall enhancement left MCA, right PCA	CT and MRI: no acute findings, frontotemporal brain atrophy	CT: no acute findings, frontotemporal brain atrophy, high-grade stenosis of right internal carotid artery	CT: no relevant findings MRI: three microbleeds with unspecific distribution (parietal lobe, right temporal lobe)	CT (admission): left lenticulostrial infarction, distal stenosis of M1 segment left MCA MRI (follow up): multiple bilateral early subacute ischemic lesions in different vascular territories, ubiquitous microbleeds, i.a. bi-thalamic, corpus callosum, periphery MRI (follow-up VWI): Marked bilateral vessel wall enhancement	CT (admission): acute ischemic lesion left precentral gyrus, microbleeds right centrum semiovale, right superior frontal gyrus MRI (follow up): multiple bilateral small early subacute ischemic lesions in both MCA territories, microbleeds in atypical locations MRI (follow-up VWI): marked vessel wall enhancement right MCA	CT: Right frontal subarachnoid haemorrhage with frontal lobe swelling, minor intraventricular blood bilaterally MRI: Additional minor left frontal and right parietal subarachnoid haemorrhage, supra- and infratentorial microbleeds with a predominantly hypertension related pattern

EEG	NA	Severe generalized background slowing (Delta) reactivity to pain: none EEG follow-up (+5d): persistent diffuse background slowing (Theta)	Bilateral rhythmic theta activity superimposed by myogenic artefacts due to myoclonic status epilepticus. Reactivity to pain: none	Moderate generalized background slowing (theta/delta). Reactivity to pain: yes (background activation).	Moderate generalized background slowing (theta/delta). Reactivity to pain: yes (background activation). Follow-up (+6d): background slowing. Periodic discharges on stimulus (SIRPIDS)	Moderate generalized background slowing (theta/delta). FIRDA. Reactivity to pain: yes (background activation). Follow-Up (+14d): mild background slowing (Theta).	Severe generalized background slowing (Delta) reactivity to pain: yes (background activation)	Severe generalized background slowing (Delta and burst suppressions)
Type of CNS disorder	Small vessel disease	Small vessel disease	Hypoxia induced	Metabolic/-toxic	Small vessel disease	Large and small vessel disease	Large and small vessel disease	Small vessel disease
Outcome at ICU discharge	Died from multi- organ failure. Autopsy: multiple small brain tissue bleedings	Still hospitalized, memory and concentration problems	Still hospitalized, awake, alert, persistent myoclonic movements	Died	Still hospitalized, moderate tetraparesis, temporarily delirious, slightly disoriented	Still hospitalized, slight tetraparesis, temporarily delirious, slightly disoriented	Still hospitalized, temporarily delirious, slightly disoriented	Still hospitalized, awake, not alert, severe tetraparesis

CNS, central nervous system; CPR, cardiopulmonary reanimation; CSF, cerebrospinal fluid; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; EEG, electroencephalography; FIRDA, frontal intermittent rhythmic delta activity, HIT, heparin induced thrombocytopenia; ICU, intensive care unit; IMV, invasive mechanical ventilation; MCA, middle cerebral artery; MRI, magnetic resonance imaging; NA, not available; PCA, posterior cerebral artery; SIRDIPS stimulus-induced rhythmic periodic, or ictal discharges; SPO_2, oxygen saturation; VWI, intracranial vessel wall sequence MRI; * Concomitant condition: additional findings which occurred at the time of the neurological deficits

Table 3: Laboratory Findings of Patients with CNS disorders in the Course of the Disease

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Relevant pathological laboratory values at time of CNS disorder	Lymph 1.82 /L, CRP 83 mg/L, IL-6 594 ng/L, fibrinogen 6.3 g/L, D-dimer > 20mg/L, thromb 96 /L	Lymph 2.47 /L, CRP 32 mg/L, IL-6 24.1 ng/L, fibrinogen 5.8 g/L, D-dimer 3.38 mg/L	Lymph 1.12 /L, CRP 29 mg/L, IL-6 15.2 ng/L, fibrinogen 5.2 g/L, D-dimer 8.59 mg/L	Lymph 3.3 /L, CRP 116.0 mg/L, IL-6 73.0 ng/L, fibrinogen 8.1 g/L, D-dimer 5.01 mg/L, thromb 83 /L, creatinine 353 umol/L, urea 30.1 mmol/L	Lymph 1.03 /L, CRP 121.0 mg/L, IL-6 131.8 ng/L, fibrinogen 5.4 g/L, D-dimer 14.59 mg/L	Lymph 1.22 /l, CRP 91.0 mg/L, IL-6 85.2 ng/L, fibrinogen 6.3g/L, D-dimer 5.05 mg/L	Lymph 1.86 /L, CRP 8.0 mg/L, IL-6 6.4 ng/L, fibrinogen 4.5 g/L, D-dimer 7.86 mg/L	Lymph 2.25 /L, CRP 240 mg/L, IL-6 21 ng/L, fibrinogen 5.8 g/L, D-dimer 2.6 mg/L
DIC score *	6	2	2	3	3	2	2	3
Time from first CNS symptoms to lumbar puncture	2	1	6	2	3	31	0	2
CSF main findings	NA	Cell count 1/ul, normal chemistry, SARS-CoV2 RT-PCR negative, no intrathecal SARS-CoV2 IgG synthesis, IL-6 in CSF < IL-6 serum	Cell count 1/ul, protein 845 mg/l, albumin 392 mg/l, SARS-CoV2 RT-PCR negative, no intrathecal SARS-CoV2 IgG synthesis, IL-6 in CSF < IL-6 serum, viral metagenomic analysis negative	Cell count 1/ul, normal chemistry, SARS-CoV2 RT-PCR negative, no intrathecal SARS-CoV2 IgG synthesis, IL-6 in CSF < IL-6 serum	Cell count 2/ul, protein 731 mg/l, SARS-CoV2 RT-PCR negative, no intrathecal SARS-CoV2 IgG synthesis, IL-6 in CSF < IL-6 serum	Cell count 1/ul, normal chemistry, SARS-CoV2 RT-PCR negative, no intrathecal SARS-CoV2 IgG synthesis, IL-6 in CSF < IL-6 serum	Cell count 0/ul, normal chemistry, SARS-CoV2 RT-PCR negative, no intrathecal SARS-CoV2 IgG synthesis, IL-6 in CSF < IL-6 serum, viral metagenomic analysis negative	Cell count 8/ul, SARS-CoV2 RT-PCR negative, no intrathecal CoV2 IgG synthesis
Type of CNS disorder	Small vessel disease	Small vessel disease	Hypoxia induced	Metabolic/-toxic	Small vessel disease	Large and small vessel disease	Large and small vessel disease	Small vessel disease

CNS, central nervous system; CSF, cerebrospinal fluid; DIC, disseminated intravascular coagulopathy; Lymph, lymphocyte count in $x10^9$/L; NA, not available; thromb, thrombocyte count in $x10^9$/L

* DIC score according to International Society on Thrombosis and Haemostasis CRRT continuous renal replacement therapy

Figures

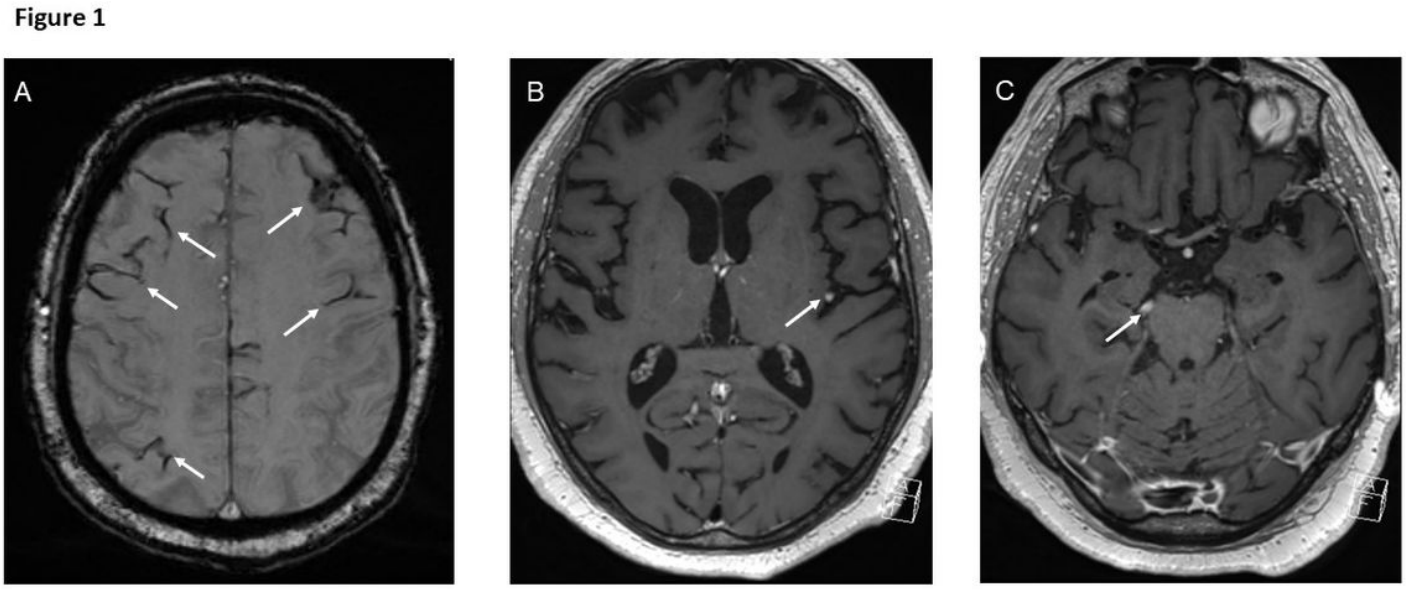

Figure 1

Illustration of the characteristic MRI findings in patient 2. Susceptibility-weighted imaging (SWI) shows subarachnoid haemorrhage on various bilateral locations (A). Intracranial vessel wall imaging (VWI) demonstrates vessel wall contrast enhancement of the left MCA (B) and right PCA (C)

Figure 2

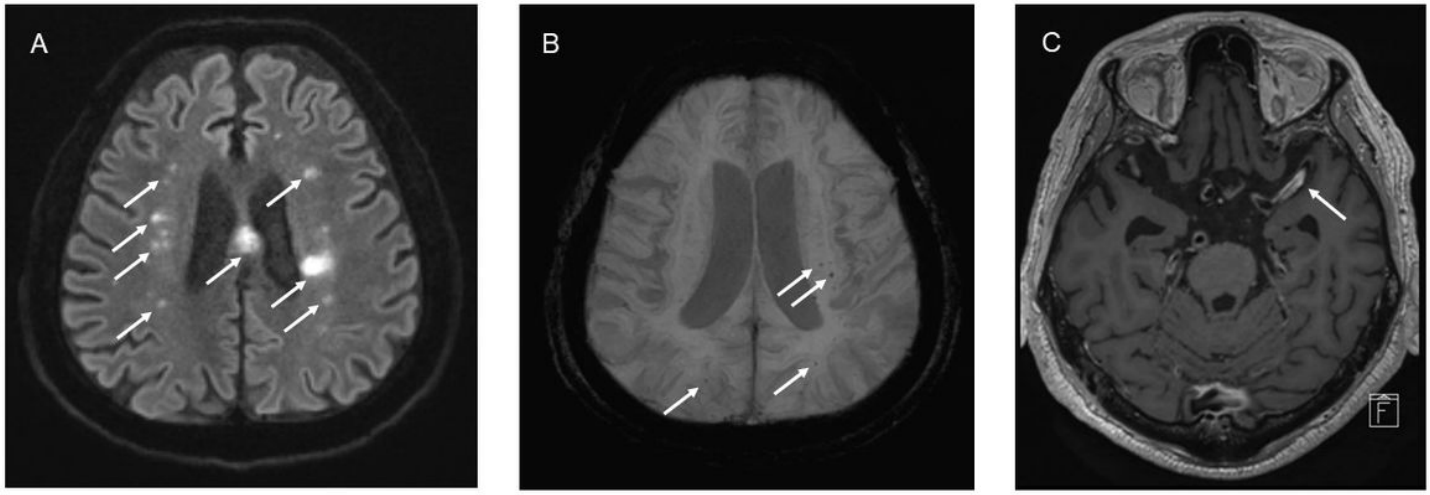

Figure 2

Illustration of the characteristic MRI findings in patient 6. Diffusion weighted imaging (DWI) shows bilaterally multiple early sub-acute ischemic lesion in different vascular territories (A) and ubiquitous microbleeds in susceptibility-weighted imaging (SWI) (B). Intracranial vessel wall imaging (VWI) demonstrates vessel wall contrast enhancement of the left MCA (C)