Neurological symptoms described in COVID-19 infected patients can also occur in a more inflammatory related setting as in case of posterior reversible encephalopathy syndrome (PRES) that can be associated with SARS-CoV2 infection due to the massive cytokine storm, damage to endothelium and vasogenic oedema. At brain imaging, quite symmetric bilateral focal or confluent vasogenic oedema with posterior parietal and occipital lobe involvement are found. In severe cases like in COVID-setting, PRES can be complicated by ischemia or haemorrhage: we then describe in the atlas two cases of classic and complicated COVID-related PRES.

Another severe complication of SARS-CoV-2 infection can be meningo-encephalitis due to hypoxic/metabolic alterations in a virus-triggered inflammatory response setting. Altered consciousness, seizures, coma are key clinical features. Neuroimaging reveals cortical and subcortical T2/FLAIR signal alterations. Even if SARS-CoV2 is rarely detected in cerebrospinal fluid (CSF), in presence of suggestive clinical and imaging findings, especially if associated with anosmia or dysgeusia, diagnosis of COVID-related meningoencephalitis can be done, as extensively discussed in Chap. 2.

4.1 Posterior Reversible Encephalopathy Syndrome (PRES) in COVID-19 Setting

Posterior reversible encephalopathy syndrome (PRES) is characterized by acute onset of severe headache (25–55% of cases), nausea and vomiting, alterations in consciousness, partial or generalized seizures, status epilepticus (75–85% of cases) and visual disturbances (20–40%) [1–4]. PRES happens more frequently in young to middle-aged people, with a women predominance. If promptly diagnosed and appropriately treated, PRES can be, completely reversible in days–weeks. However, there can be irreversible severe complications like brainstem involvement, ischemia and haemorrhagic transformation, responsible for long-term neurological deficits or even death.

PRES can be triggered by different clinical entities: the most common aetiologies are (pre-)eclampsia, infection, sepsis, shock, hypertension, autoimmune disease, immunosuppressive treatments [1–4].

The pathogenesis of PRES is not exactly known.

Three main pathogenetic theories for PRES have been proposed, each of them has some limitations.

1. “Breakthrough theory”: rapidly developing hypertension causes a breakdown in brain auto-
regulation leading to blood–brain barrier (BBB) collapse, hyper perfusion with protein and fluid extravasation and vasogenic oedema [5, 6].

2. “Vasospasm theory”: PRES is caused by vasospasm with subsequent ischemia (overlap with Reversible cerebral vasoconstriction syndrome, RCVS) [5, 6].

3. “Toxic theory”: PRES is triggered by endothelial damage caused by endogenous or exogenous toxins (preeclampsia, sepsis) [6, 7] via increased leukocyte trafficking, decreased production of endothelium-derived vasorelaxants and disproportioned release of proinflammatory and vasoconstrictive cytokines [8–13].

COVID-19 infection and PRES share multiple risk factors, responsible for loss of homeostatic regulation of blood flow to the brain, increased susceptibility to blood pressure changes and brain oedema [14, 15].

1. Renal failure is a strong predictor of the development of PRES (up to 55% of cases) [16]. The cytokine storm (fever, increased levels of ferritin, IL–6, TNF-α, LDH, CRP, D-dimer), typical of SARS-CoV2 infection, may be also responsible or associated with development of PRES, by means of blood–brain barrier (BBB) breakdown, increased vascular permeability and upregulation of vascular endothelial growth factor (VEGF) in hypoxic condition [14, 16].

2. Labile arterial blood pressure. Many cases of PRES in COVID-19 are seen in patients with relatively moderate blood pressure fluctuations as a possible consequence of SARS-CoV2-induced endothelial dysfunction.

3. Endothelial injury, key factor in PRES, is part of COVID-19 spectrum: SARS-CoV2, by means of the spike protein S1, binds to the angiotensin-converting enzyme 2 (ACE2) receptor leading to an increase in blood pressure and alteration of the endothelial layer [14, 17].

4. Hypoxia is a well-known trigger of inflammation at local and systemic levels [14, 18, 19].

5. Immunomodulatory-like and monoclonal drugs such as tocilizumab, known to induce PRES by means of endothelial modulation properties, are largely used in COVID-19 patients [20, 21].

PRES-associated haemorrhages, more frequent in COVID-19 setting, can be explained by coagulopathy, often in terms of disseminated intravascular coagulation syndrome with liver dysfunction and consumption of clotting factors [14].

As pure clinical diagnosis of PRES can be challenging, imaging is mandatory also in a prognostic fashion.

### 4.1.1 Brain Imaging in COVID-Related PRES

In case of COVID-19 infection the imaging presentation of PRES doesn’t differ from the typical one, but in the published cases seems to be more extensive.

At CT and MRI, PRES is characterized by a symmetric bilateral vasogenic oedema with classic posterior parietal and occipital lobe involvement [22] (the middle cerebral artery (MCA)–posterior cerebral artery (PCA) border zone). Calcarine and paramedian occipital lobe is usually spared. Subcortical white matter and cortical grey matter can be involved, depending upon the severity of the disease. CT is less sensitive than MRI in detecting the initial findings, with a normality rate of CT around 22% [2, 22, 23]. The most sensitive MRI sequence is Fluid Attenuated Inversion Recovery (FLAIR). Diffusion-weighted (DWI) is pivotal to distinguish classic and reversible PRES (vasogenic oedema, high signal on apparent diffusion coefficient–ADC–map) from complicated, irreversible cases (cytotoxic ischemic oedema, high signal on DWI, low signal on ADC map). Quantitative assessment of ADC maps can detect mild alterations [24]. DWI can be very useful in the prediction of irreversible tissue damage. Diffusion-tensor imaging (DTI) reveals anisotropy loss in posterior regions [24]. At magnetic resonance spectroscopy imaging (MRS) [25] there are slowly reversible metabolic abnormali-
ties with increased choline and creatinine levels and mildly decreased N-acetyl aspartate in normal and abnormal appearing brain regions on conventional MRI sequences.

The main patterns of PRES include:

1. Parieto-occipital dominance (typical) [2, 23, 26].
2. Holo-hemispheric involvement at watershed zones (anterior cerebral artery [ACA]/MCA/PCA border zones) [23, 26].
3. Superior frontal sulcus distribution (ACA/MCA border zones): isolated involvement of mid and posterior aspect of superior frontal sulcus [2, 23, 26].
4. Central variant (<5% of cases) with involvement of temporal lobes, deep white matter, basal ganglia, brainstem, splenium of corpus callosum and cerebellum [26].
5. Overlapping or asymmetric expression of the previous-described patterns.

Imaging findings are usually reversible in days to weeks after treatment. In severe cases (around 15–20% of patients), PRES may progress to infarction (cytotoxic oedema with diffusion restriction, low ADC values) or haemorrhage, both petechial and intraparenchymal (hypointensity areas on Gradient Echo (GRE) T2* or Susceptibility-Weighted Imaging (SWI) sequences). Parenchymal or leptomeningeal contrast enhancement may be seen in subacute phase. If complicated or in cases of brainstem involvement, PRES tends to be irreversible with parenchymal damage resulting in encephalomalacia [2, 23, 26, 27].

In most patients with PRES (85%) there are overlapping features with RCVS (Reversible cerebral vasoconstriction syndrome) characterized by reversible focal vasoconstriction, vasodilatation and “string of bead” appearance of medium and small arteries, revealed by CT Angiogram (CTA) or catheter angiography [23, 28].

The main imaging differential diagnoses of PRES, based on the distribution of the lesions, are:

(a) Hypoxic ischemic encephalopathy: similar pattern of oedema. Involvement of the deep grey matter is peculiar in HIE [29].
(b) Bilateral subacute posterior border-zone infarcts: unilateral vascular distribution, cytotoxic oedema [29–31].
(c) Basilar top syndrome: involvement of medial occipital lobe and thalami.
(d) Vasculitis: reversibility of PRES lesions might be of help.
(e) Reversible brain oedema in post-ictal state and seizures: hippocampi and splenium of corpus callosum are usually involved [23].
(f) Encephalitis: involvement of grey and white matter.

4.1.2 Case Description

In this chapter, we extensively present clinical cases as we faced them: clinical setting first and images as last of this chapter.

4.1.2.1 Case 1

In April 2020, a previously healthy 56-year-old man presented with 10 days of dyspnoea, headache, fever, and cough. He tested positive for COVID-19 and was treated with hydroxychloroquine and steroids. Blood pressure range was 145–190/80–95 mmHg, with no metabolic derangements.

After days of hospitalization, due to persistence of altered mental status in spite of weaning sedation, brain CT scan revealed cortico-subcortical mild hypodensity with swelling involving right anterior-middle aspect of frontal lobe, right posterior parietal lobe and left temporoparietal region. No haemorrhagic contamination was seen. No evidence of intracranial arterial malformations or venous sinus thrombosis was seen at CT arterial and venous angiogram (not shown).

A brain contrast-enhanced MRI done after days of hospitalization revealed cortico-subcortical predominant white matter T2 and FLAIR hyperintense signal alterations in right anterior-middle aspect of frontal lobe, right posterior parietal lobe, left temporoparietal region, and, in a lesser extent, left middle frontal area. There was hyperintensity on DWI (T2-shine through effect) with no diffusion restriction on ADC map and no haemorrhage in keeping with
vasogenic oedema in a typical plus superior frontal sulcus pattern of PRES. No alterations were seen of magnetic resonance angiogram. After Gadolinium, there was mild punctate and linear enhancement in the previously described areas especially in right fronto-parietal regions, in keeping with BBB injury. On Day 20 since hospitalization, he had seizures with rightward gaze deviation and right arm and leg shaking. He was treated with levetiracetam and valproic acid. His mental status improved during the following weeks. Patient was discharged after 3 weeks of hospitalization in discrete clinical conditions (Figs. 4.1 and 4.2).

4.1.2.2 Case 2
At the beginning of March 2020, a 21-year-old young man affected by Alport syndrome (with mildly elevated creatinine levels) accessed to our emergency department referring 5 days of dyspnea, headache, fever, and dry cough. He tested positive for SARS-CoV2 virus on a nasopharyngeal swab. He was treated with hydroxychloroquine and steroids. His hospital course was complicated with mild respiratory failure requiring CPAP positioning. On hospital Day 15, an un-enhanced head MRI was obtained because of persistently poor mental status and revealed typical bilateral and quite symmetric cortical-subcortical T2-FLAIR signal hyperintensity with high signal in DWI and in ADC map in temporo-occipital regions and in posterior and mesial aspect of parietal lobe. Anterior and middle lateral aspects of frontal lobes, especially on the right-hand side, were also involved (superior frontal sulcus pattern). Punctate hyperintense lesions in right cerebellar hemisphere. No haemorrhagic components. These findings were in keeping with PRES alterations with typical posterior pattern associated with superior frontal sulcus involvement.

His mental status slowly improved. Patient was discharged after 4 weeks of hospitalization in good clinical conditions (Fig. 4.3).

4.1.3 Discussion
We described two cases of COVID-related PRES. First case showed a complicated PRES brain involvement with BBB damage expressed by punctate leptomeningeal and cortical contrast enhancement. The second one is a classic case of non-complicated PRES without cytotoxic oedema or haemorrhage. Anyway, in both cases there is a mixed pattern of PRES, with typical posterior regions involvement associated with superior frontal sulcus pattern.

Fig. 4.1 Axial slices of brain non-contrast CT scan (16/04/20). Cortico-subcortical mild hypodensity with swelling involving right anterior-middle aspect of frontal lobe, right posterior parietal lobe and left temporo-occipital region
Fig. 4.2 Brain contrast-enhanced MRI scan (17/04/20). Cortico-subcortical T2-FLAIR hyperintense signal alterations in right anterior-middle aspect of frontal lobe, right posterior parietal lobe, left temporo-occipital region and, in a lesser extent, left middle frontal area. Hyperintensity on DWI (T2-shine through effect) with no diffusion restriction on ADC map and no haemorrhage (GRE sequence not shown). Mild punctate and linear enhancement especially in right fronto-parietal regions.

From left to right and from upward to downward:
- First row: axial T2-weighted sequences (two slices), axial diffusion-weighted imaging (DWI)
- Second row: axial fluid attenuated inversion recovery (FLAIR) sequences (two slices), axial apparent diffusion coefficient (ADC) map (ADC)
- Third row: axial post-Gadolinium T1-weighted sequences (two slices), coronal post-Gadolinium T1-weighted sequence
About 30 cases of PRES have been described since February 2020 in patients with positive SARS-CoV2 swab and congruous clinical and imaging pattern. To be mentioned is also a PRES case seen during postmortem imaging [32] in a COVID-19. According to the Literature, the majority of PRES patients had severe respiratory manifestations of COVID-19 requiring intensive respiratory support. PRES can develop also in asymptomatic COVID-19 patients [33]. The high number of COVID-19-related PRES cases can be also due to large use of interleukin 1 and 6 inhibitors (Anakinra and Tocilizumab) in COVID-19 therapy: these drugs can directly act on endothelial function favouring typical PRES alterations [20, 34–37]. In 60% of patients with clinically suspected PRES brain MRI was normal. In about 40% of cases, typical PRES pattern is seen with often mild, posterior, bilateral, quite symmetric oedema [33]. In COVID-19 setting, as seen in our cases, there is an increased rate (10–30% of patients) of deep white matter, basal ganglia and cerebellum involvement as well as haemorrhagic contamination [14, 38, 39], cytotoxic oedema (diffusion restriction) and increased parenchymal and leptomeningeal contrast enhancement in a holo-hemispheric distribution with frequent basal ganglia and cerebellar involvement [14, 39].

Due to higher rate of complications, in all COVID-19 patients with suspected PRES it is pivotal to acquire GRE T2* or, better, SWI sequences (to reveal small and punctate haemorrhagic foci) and MRA in addition to the other morphologic sequences and DWI.

### 4.2 Meningo-Encephalitis in COVID-19 Setting

Viral meningoencephalitis is the result of human virus affecting brain and meninges and can involve any age group [40]. The prodrome of encephalitis is often nosophic; the patients show neurologic manifestation such as fever, headache, nausea and vomiting, seizures and unconsciousness, altered sensorium, neurological deficit and coma. Many encephalitis cases have high morbidity and mortality.

With encephalopathy we mean a diffuse brain dysfunction of toxic, metabolic, hypoxic-ischemic, septic, inflammatory or immune-mediated aetiology. Primary encephalitis is due to direct involvement of CNS, while in secondary/post infectious encephalitis there is a CNS spreading of a viral infection located elsewhere in the body [40].

In viral encephalitis, some viruses are neurotropic (they specifically target the brain, spinal cord and/or peripheral nerves), others cause unselective collateral damage to CNS. The neurotropic viruses may reach the CNS by haematogenous, cerebrospinal fluid (CSF) or neural route e.g. Herpes Virus [41].

Brain damage in viral encephalitis results from the intracellular virus proliferation and from host inflammatory-immune response, against the virus or the infected cells.

The diagnosis is based on laboratory investigations on CSF analysis; neuroimaging has a critical and important role in early diagnosis and for follow-up [42].

---

**Fig. 4.3** Brain MRI scan (24/03/20). Typical bilateral and quite symmetric cortical-subcortical T2-FLAIR signal hyperintensity with high signal in DWI and in ADC map in temporo-occipital regions and in posterior and mesial aspect of parietal lobe. Anterior and middle lateral aspects of frontal lobes, especially on the right-hand side, were also involved (superior frontal sulcus pattern). Punctate hyperintense lesions in right cerebellar hemisphere. No haemorrhagic components

**From upward to downward:**
- First row: axial fluid attenuated inversion recovery (FLAIR) sequences (three slices)
- Second row: axial T2-weighted sequences (three slices)
- Third row: axial diffusion-weighted imaging (DWI) (three slices)
- Fourth row: axial apparent diffusion coefficient (ADC) map (ADC) (three slices)
Magnetic resonance (MR) might reveal non-specific findings as vasogenic brain oedema and local or diffuse swelling, haemorrhages, necrosis and different patterns of enhancement, i.e. parenchymal and/or leptomeningeal [40, 43]. At macroscopic pathologic analysis, there are reduced transparency of the meninges, vascular congestion and local or diffuse swelling; microscopically infiltration by inflammatory cells is found [42].

Around 15 viral families (about 100 viruses) plus a non-viral agent (prion) may infect CNS [43, 44]. Certain viruses have a particular affinity for specific CNS cells (meningeal cells, oligodendrocytes, astrocytes and neurons) due to their cell-surface properties: based on the location of the signal abnormality, specific MRI diagnosis can be achieved [40, 42].

Herpes viruses replicate in neuronal and glial cells of the limbic system [41]; JC virus mainly involves oligodendrocytes in the thalamus, basal ganglia, cerebral cortex [45, 46]; Coxsachie involve the midbrain [47], Echo viruses, meningeal and ependymal cells [47].

Clinical presentation varies from asymptomatic to rapidly progressive and severe also with fatal outcome. Often, the severity of disease is not related to the virus itself but to the host inflammatory-immune systemic response the viral agent can trigger [40, 42].

The most common and early neurological manifestations in COVID-19 are myalgias, headache, dizziness, anosmia and dysgeusia. More severe symptoms of COVID-19 associated encephalitis/encephalopathy are fever, headache, seizure, focal neurological deficits, delirium, altered consciousness and coma [48, 49].

According to a retrospective review of 841 hospitalized patients with COVID-19 (mean age: 66.4 years), 57% had a neurological symptom [49, 50]. Altered consciousness (about 20% patients) usually occurs in old patients with severe disease [51]. Generalized myoclonus, aggravated by auditory and tactile stimuli, was described in severe cases of COVID-19-related CNS involvement: a post-infectious autoimmune pathogenesis was suspected [52].

MRI features of SARS-CoV-2-associated meningoencephalitis are nonspecific, congruous with a diffuse brain inflammatory condition: poorly delineated focal or diffuse T2/FLAIR hyperintensity of superficial and deep grey matter and/or white matter, basal ganglia/thalamus, areas of oedema, diffusion restriction, patchy haemorrhage, necrosis and variable enhancement can be found [53].

In COVID-19 associated encephalitis, CSF examination may show inflammatory changes (increased protein and/or cells). The presence of the virus SARS-CoV-2 within the CNS is related to neuro-invasiveness/ neuro-tropism (the virus capacity to reach the CNS) and neurovirulence (the virus capacity to actively proliferate within the CNS). SARS-CoV-2 can enter the CNS via hematogenous dissemination or via retrograde pathway along olfactory nerves [54–56].

As other genetically similar neurotropic coronaviruses (HCoVs, SARS-CoV16, SARS-CoV27, SARS-CoV1), but with higher affinity, SARS-CoV2 enters a neural cell using the cell membrane-bound human angiotensin-converting enzyme 2 (ACE) receptor, widely expressed in the glial cells and in the brain stem nuclei with cardiorespiratory regulating effects [57, 58]. After ACE receptor binding, a cytokine storm is triggered with an important inflammatory response, blood–brain barrier breakdown [59] and increased destructive effects on CNS. Another possible pathogenetic mechanism involves a secondary hemophagocytic lymphohistiocytosis (sHLH) development resulting in a hyperinflammatory syndrome with fulminant hypercytokinemia responsible for fatal sepsis and multiorgan failure [60–62].

Plasmaferesis or hyperimmune plasma injection has been used as a treatment, with significative results [63, 64].

4.2.1 Case Description

4.2.1.1 Case 1

A 76-years-old male, with a previous history of arterial hypertension, atrial fibrillation in therapy, peripheral vascular disease, was taken to the
emergency department due to fever, dyspnoea, severe respiratory failure, altered mental status and coma. He was intubated the next day. During hospitalization he developed kidney failure requiring dialysis, important anaemia with need for blood transfusions, peripheral motor sensory polyneuropathy, episodes of atrial flutter. His clinical conditions were complicated with a septic shock, requiring vasopressor and multiple antibiotics. Chest CT scan revealed diffuse interstitial pneumonia; COVID-19 swab was positive.

First brain CT was normal. At neurological examination he had discreet plastic hypertonus, with hints of asterixis. On a follow-up CT scan showing a diffuse hypodense alteration affecting the bi-hemispheric subcortical white matter, especially at the level of the semi-oval centres with associated multiple hypodense cortical-subcortical alterations. Brain MRI (see below) scan revealed diffuse signal alteration in keeping with encephalitic picture; the involvement of both thalami and the presence of both hemosiderin deposits and focal areas of diffusion restriction is consistent with acute necrotizing encephalopathy. At cerebrospinal fluid assessment with chemical-physical and cytological examination there were five nucleated elements, proteins >125, glucose value of 64. CFS PCR resulted positive for SARS-CoV-2. Under the suspicion of post viral autoimmune encephalitis, he underwent IV immunoglobulin G therapy for four cycles at a dose of 0.4 g/kg for 5 days, with progressive slow improvement of clinical conditions. He was discharged from the hospital after about 3 months of hospitalization with a final diagnosis of SARS-CoV-2 related necrotizing encephalitis (Figs. 4.4, 4.5, 4.6, and 4.7).

**4.2.1.2 Case 2**

A 56-year-old man, with a previous history of arterial hypertension was taken to the emergency department due to dyspnoea, severe respiratory failure, altered mental status, increasing seizures and coma. He was immediately intubated. He developed septic shock, requiring vasopressor and various lines of antibiotics. Chest CT scan (not shown) revealed interstitial pneumonia; COVID-19 swab was positive.

At neurological examination he had plastic hypertonus. Urgent brain MRI (10/04/20) showed marked and diffuse T2-FLAIR hyperintensities with significant swelling involving the grey and white matter of bilateral fronto-parietal, temporoccipital, temporopolar regions and left posterior cingulum with striking left prevalence. Moreover, right thalamus, left thalamus and internal capsule, splenium of the corpus callosum (with left prevalence), left cerebellar hemisphere and vermis are affected. In all described regions there is diffusion alteration with significant restriction, hypointense on ADC map, especially in the right portion of the splenium, left cingulum and temporo-occipital lobe, consistent with mixed vasogenic and cytotoxic oedema.
Fig. 4.5 Axial slices of Brain CT (20/04–28/04/20). In the first exam (upper row) no actual pathologic findings; post-traumatic porencephalic left frontal area. Follow-up exam (lower row) shows diffuse infra and supratentorial white matter hypodense alteration with sparing of U-fibres and cortical layer.

Fig. 4.6 Brain contrast-enhanced MRI scan (29/04/20). Diffuse quite symmetric T2-FLAIR hyperintensity involving infra and supratentorial white matter with a predominant periventricular distribution with increased diffusion; corpus callosum and bilateral thalamic involvement (>right); punctate haemorrhagic foci are seen in right temporo-occipital region, thalami (>left) and cerebellar hemispheres. Small right parietal ischemic lesions. No significant contrast enhancement after Gadolinium injection. No vascular malformations.

From upward to downward:
- First row: axial T2-weighted sequences (three slices);
- axial fluid attenuated inversion recovery (FLAIR) sequences (three slices)
- Second row: axial T2-weighted sequences (three slices)
- Third row: axial diffusion-weighted imaging (DWI) (three slices)
- Fourth row: axial apparent diffusion coefficient (ADC) map (ADC) (three slices)
Posterior Reversible Encephalopathy Syndrome (PRES) and Meningo-Encephalitis in COVID
Fig. 4.7  Disease follow-up with brain contrast-enhanced MRI scans (29/04–20/05–13/07/20). Progressive improvement of brain white matter alterations. Minimal residual atrophy

From upward to downward:

- First and second rows: axial fluid attenuated inversion recovery (FLAIR) sequences (different levels)
- Third row: axial T2-weighted sequences (three slices)
Haemorrhagic methaemoglobin-hemosiderin contamination (mildly hyperintense on T1 and hypointense on T2-GRE T2*) was found in left temporo-occipital and cerebellar areas. Cortical laminar necrosis and faint contrast enhancement in keeping with altered BBB can be also appreciated. There was significant mass effect with right-sided midline shift, trans-falcine cingular gyrus herniation, right displacement of fourth ventricle and brain stem and downward position of cerebellar tonsils. Imaging findings were in keeping with severe acute haemorrhagic encephalitic pattern.

On brain CT scan performed after 10 days due to clinical worsening with ataxia and cerebellar signs, there was a huge oedematous left cerebellar parenchymal hematoma (about 45 × 30 mm) with signs of different age bleeding. Diffuse cortico-subcortical hypodensity and punctate haemorrhagic lesions were also seen.

Follow-up brain MRI performed after 15 days, in the previously involved brain areas there was diffuse cortico-subcortical atrophy with malacic alterations and diffuse cortical laminar necrosis (T1 cortical hyperintensity) and BBB residual breakdown with faint contrast enhancement. Normal evolution of the left hemispheric cerebellar hematoma. Oedema and mass effect are quite completely resolved with e-vacuo enlargement of the lateral ventricles.

At cerebrospinal fluid assessment with chemical-physical and cytological examination there were some nucleated cells, proteins >150, glucose value of 72. CSF PCR tested positive for SARS-CoV2. He underwent IV immunoglobulin G therapy for three cycles at a dose of 0.4 g/kg for 5 days, with slow improvement of clinical conditions (Figs. 4.8, 4.9, 4.10, and 4.11).

4.2.1.3 Case 3
A 56-year-old male, HCV positive. In March 2020, he was taken to emergency department after being found in coma but spontaneously breathing. He was intubated at home. First two nasopharyngeal SARS-CoV-2 swabs were negative. He was admitted to Intensive Care Unit.

Brain CT and EEG were negative; chest CT revealed compact parenchymal consolidation with air bronchogram and scissure delimitation in the basal-posterior and superior segments of the inferior lobes. On the right, consolidation involved also the anterior, posterior and apical portions of the upper lobe. Diffuse peribronchovascular infiltrates with predominantly ground glass patterns are associated, with relative sparing of the lower parts of the middle lobe and lingula.

Due to massive increase of inflammatory indices (PCT 158, PCR 45), he was treated with Piperacillin/Tazobactam + Metronidazole then replaced with Amoxicillin/Clavulanate + Clarithromycin, with slow improvement of clinical picture.

Then, hospitalization complicated with sepsis and Crush syndrome with renal insufficiency (and hepatic insufficiency). He remained in a state of coma (opening eyes to painful stimulus, hint of flexion). Due to persistent severe respiratory failure, repeated BAL tested positive for SARS-CoV-2 (on 24/3/2020). Subsequent BAL of 18/4 and 23/4 were negative.

Brain CT revealed diffuse supratentorial periventricular and corona radiata white matter hypodensities with no haemorrhagic components.

During hospitalization in infectious diseases unit he was put on CPAP. He was then transferred in intensive care unit and intubated again due to infection and septic shock. Blood cultures were positive for Enterococcus faecium treated with Linezolid with benefit (suspended on 20/4).

Brain MRI with MR angiography revealed supratentorial white matter, especially in bilateral frontal and parietal regions, with sparing of the U-shaped fibres, showed altered T2-FLAIR hyperintense signal with increased diffusion. On SWI sequence there were multiple deposits of haemoglobin degradation products in the posterior fossa and in the supratentorial compartment both in brain tissue (including the corpus callosum) and in the subarachnoid spaces. Gliotic-malacic ischemic stabilized ischemia in the right pallidum. Compared to the previous CT scan there was a progressive enlargement of the supratentorial ventriciles. No areas of contrast enhancement. There was marked hypotrophy of olfactory bulbs with left prevalence.
The findings were in keeping with COVID-related encephalopathy with marked atrophy: no specific therapies were done (Figs. 4.12, 4.13, 4.14, and 4.15).

4.2.1.4 Case 4

A 56-year-old male, with previous history of arterial hypertension in therapy with olmesartan 20 mg/day, chronic cerebral vasculopathy and mild cognitive impairment, on 1/5/20 was found unconscious on the ground at home feverish with sphincter release. He was taken to our emergency department where he performed un-enhanced brain CT revealing bilateral subarachnoid haemorrhage, especially in the cingular region (>left). Moreover, there are some hypodense periventricular (>posterior) white matter alterations, in keeping with chronic cerebral vasculopathy and bilateral capsulo-lenticular stabilized ischemic lesions. Mild enlargement of the ventricular system. Subsequent CT angiogram (not shown) was normal.

Chest X-ray showed diffuse confluent interstitial-alveolar alterations in both lungs with relative sparing of the apical regions.

Antibiotic therapy with ceftriaxone and azithromycin (continued for 5 days) associated with methylprednisolone (1 mg/kg for 5 days then gradually decreasing) was started. He was intubated with good respiratory exchanges.

At blood tests: white cells 7380 (6320 neutrophils), Haemoglobin 15, platelets 134, AST 81, ALT 49, LDH 468; SARS CoV2 nasopharyngeal swab was positive. The patient was enrolled in the study protocol for Remdesivir drug, administered for 10 days. He also underwent hyperimmune plasma experimental treatment. In the following days there was a clinical worsening with progressive disorientation and expressive aphasia, after neurological consult, diagnostic lumbar puncture was performed: at CSF exam there were 2000 red cells, glycorrhachia and protdorrachia were normal. PCRs for herpes viruses, enteroviruses and SARS-Cov2 were negative. EEG showed globally slowed activity.

Brain MRI with MRA (08/05/20) revealed diffuse confluent supratentorial periventricular and deep white matter T2-FLAIR high signal intensity alteration with increased diffusion and mild increased perfusion. Left callosal area of contrast enhancement and haemorrhagic contamination. Diffuse punctate infra and supratentorial white matter micro haemorrhagic–microthrombotic lesions. Small acute ischemic lesions in the posterior middle third of the left corona radiata. Olfactory bulbs were hypotrophic with left prevalence. In view of SARS-CoV-2 infection and rapid evolution of the clinical picture, findings were in keeping with haemorrhagic COVID-related encephalitis.

At follow-up brain MRI scan performed on 20/05/20 there was minimal reduction in left callosal contrast-enhanced alteration. Other findings were stable.

Fig. 4.8 Brain contrast-enhanced MRI scan (10/04/20). Marked and diffuse T2-FLAIR hyperintensities with tissue swelling involving the grey and white matter of bilateral fronto-parietal, temporo-occipital, temporo-polar regions and left posterior cingulum with left prevalence. Right thalamus, left thalamus and internal capsule, splenium of the corpus callosum (with left prevalence), left cerebellar hemisphere and vermis are affected. In all regions there is significant diffusion restriction especially in the right portion of the splenium. Haemorrhagic contamination in left temporo-occipital and cerebellar areas. Cortical laminar necrosis and faint contrast enhancement was seen. Significant mass effect with right-sided midline shift, trans-falcine cingular gyrus herniation, right displacement of fourth ventricle and brain stem and downward position of cerebellar tonsils.

From left to right and from upward to downward:
- First row: axial fluid attenuated inversion recovery (FLAIR) sequences (three slices)
- Second row: sagittal T2-weighted sequence, axial Gradient Echo T2* sequence (two slices)
- Third row: axial diffusion-weighted imaging (DWI, one slice) and apparent diffusion coefficient (ADC) map (two slices)
- Fourth row: axial T1-weighted sequences (three slices)
- Fifth row: axial, coronal and sagittal post-Gad T1-weighted sequence
Fig. 4.9 Brain multiplanar non-contrast CT scan (19/04/20). Huge oedematous left cerebellar parenchymal hematoma (about $45 \times 30$ mm) with signs of different age bleeding. Diffuse cortico-subcortical hypodensity was seen in the MRI signal alteration areas. Punctate haemorrhagic lesions were seen also in left posterior temporo-occipital and superior frontal lobe.
Fig. 4.10 Brain contrast-enhanced MRI scan (24/04/20). In the previously involved brain areas, there was diffuse cortico-subcortical atrophy with malacic alterations and diffuse cortical laminar necrosis and BBB residual breakdown with faint contrast enhancement. Normal evolution of the left hemispheric cerebellar haematoma. Quite complete resolution of oedema and mass effect with e-vacuo enlargement of the lateral ventricles.

From left to right and from upward to downward:
- First row: axial fluid attenuated inversion recovery (FLAIR) sequences (three slices)
- Second row: sagittal T2-weighted sequence, axial diffusion-weighted imaging (DWI, one slice) and apparent diffusion coefficient (ADC) map (one slice)
- Third row: axial T1-weighted sequences (three slices)
- Fourth row: axial, coronal and sagittal post-Gad T1-weighted sequence
Fig. 4.11  Comparison between MRI scan of 10/04 (left) and 24/04/20 (right)

From upward to downward:
• First and second rows: axial T2-weighted sequences
• Third row: axial T1-weighted sequences (three slices)
• Fourth row: sagittal post-Gad T1-weighted sequence
Fig. 4.12 Axial slices of chest CT (07/03/20) with lung (on the left) and mediastinum windows (on the right). Bilateral basal consolidations and ground glass alterations

Fig. 4.13 Axial slices of brain CT (07/03/20). Normal findings
The patient underwent a new diagnostic lumbar puncture on 25/05, always negative for SARS-CoV-2. His clinical conditions slowly improved: the patient was discharged after about 2 months of hospitalization.

In view of the clinical course, imaging findings and lab test a diagnosis of SARS-CoV-2-related encephalopathy/endothelitis was done. Due to the negativity of CSF viral test, a postviral immune-mediate mechanism was supposed (Figs. 4.16, 4.17, 4.18, and 4.19).

4.2.2 Discussion

Moriguchi et al. [55] and Zambreanu et al. [65] described cases of COVID-19-related meningoencephalitis with involvement of limbic system and ventriculitis. SARS-CoV-2 RNA was not detected in the nasopharyngeal swab but in CSF. Considering that in COVID associated encephalopathy brain imaging can also be completely normal [66–69], in many cases there is confluent and symmetric cytotoxic oedema (dif-
fusion restriction) in brain white matter, with sparing of subcortical U-fibres, similar to post-hypoxic leukoencephalopathy or high-altitude cerebral oedema. Leptomeningeal enhancement can be seen on post-contrast T1-weighted and fluid attenuated inversion recovery (FLAIR) sequences. Periventricular white matter T2/FLAIR hyperintensity and microbleeds can be associated in COVID-related microangiopathy setting [69].

COVID-19 is associated in about 5–25% of cases with hypoxia, silent or overt, especially in hospitalized intubated patients [70]. Silent hypoxia can be difficult to assess in particular in asymptomatic patients. However, in a recent case series [70] only one patient had clinically significantly low oxygen saturation (90%) at the time of presentation, suggesting that encephalopathy can

Fig. 4.16 Chest X-ray (01/05/20): diffuse confluent interstitial-alveolar alterations in both lungs with relative sparing of the apical regions

Fig. 4.17 Axial brain non-contrast CT scan (18/05/20). Bilateral subarachnoid haemorrhage, especially in the cingular region (>left). Moreover, there are some hypodense periventricular (>posterior) white matter alterations, in keeping with chronic cerebral vasculopathy and bilateral capsulo-lenticular stabilized ischemic lesions. Mild enlargement of the ventricular system

Fig. 4.18 Brain MRI scan (20/05/20). Diffuse confluent supratentorial periventricular and deep white matter T2-FLAIR high signal intensity alteration with increased diffusion and mild increased perfusion. Left callosal area of contrast enhancement and haemorrhagic contamination. Diffuse punctate infra and supratentorial white matter micro haemorrhagic–microthrombotic lesions. Olfactory bulbs hypotrophy with left prevalence

From left to right and from upward to downward:
- First row: axial, sagittal and coronal 3D fluid attenuated inversion recovery (FLAIR) reformatted sequences
- Second row: axial (one slice) and coronal (on olfactory bulbs) T2-weighted sequence; dynamic susceptibility contrast (DSC) perfusion map (cerebral blood volume, rCBV)
- Third row: axial Minimum intensity projection (MinIP) Susceptibility-weighted imaging (SWI)
- Fourth row: axial, coronal and sagittal post-Gadolinium T1-weighted sequences
Posterior Reversible Encephalopathy Syndrome (PRES) and Meningo-Encephalitis in COVID
occur even before a proper hypoxic status. Grey matter, basal ganglia and brain stem can be involved as well as white matter, raising the suspicion for encephalitis even in the absence of other known causative factors.

So far, some peculiar COVID-19-related encephalitis patterns have been described:

1. COVID-19 can involve predominantly the white matter of brain, brainstem and spinal...
cord with a suggested postviral demyelination mechanism, an immune-mediated inflammatory demyelinating disorder occurring within days to weeks after viral infection. In these cases, it is not the virus itself but the host-enhanced immune and inflammatory response which can damage both white and grey matter. Up to July 2020, 12 cases of possible immune-mediated encephalitis and postviral polyneuropathies have been described in COVID-19, with a mean age of patients around 40s [55, 70–73]. Clinical presentation ranged from neuropsychiatric symptoms and coma, to brainstem involvement (like Bickerstaff brainstem encephalitis), to cranial nerve palsies, to peripheral polyradiculitis like Guillain–Barré and Miller Fisher syndromes [71–74].

Severe and lethal cases of acute/fulminant acute haemorrhagic leukoencephalitis, ANE, or acute disseminated encephalomyelitis (ADEM) have been described so far [75]. Acute necrotizing encephalopathy (ANE), probably related to severe cytokine storm, is characterized by symmetrical, multiple T2-FLAIR hyperintense lesions in the thalamus, basal ganglia, deep white matter and brainstem with scattered haemorrhagic foci. Clinically, patient presents with seizures, focal neurological deficit and coma. In acute disseminated encephalomyelitis (ADEM) white matter, brainstem, optic nerves and spinal cord are variably affected [76].

In some cases, CSF pleocytosis and anti-GD1b IgG and anti-Caspr2 antibodies were found, which correlated with more severe disease and poor outcome [77, 78]. No evidence of direct SARS-CoV-2 CNS infection was found.

2. Mild encephalitis/encephalopathy with a reversible splenial lesion, already described in case of MERS [79].

3. COVID-19-associated meningoencephalitis with intracerebral haemorrhage and subdural hematoma [62].

4. Steroid-responsive encephalitis with normal brain imaging suggesting a hyperinflammatory mechanism [74].

5. COVID-related rhombencephalitis usually in a context of a wider systemic inflammatory process. This particular form of encephalitis with brainstem involvement has been associated so far with multiple sclerosis, Bechet disease, listeria monocytogenes infection, paraneoplastic syndrome, Epstein–Barr virus and tuberculosis [80]. Many cases remained of unknown origin.

In COVID-19-related encephalitis, it is challenging to demonstrate direct infection of neurons/glial cells by SARS-CoV-2 viral particles, as most of RT-PCR analyses from CSF were normal or nonspecific [81]. Only in few patients with encephalitic features test was positive [55, 82]. Anyway, in presence of clinical and MRI suggestive findings in a COVID-19 positive patient, especially if associated with anosmia or dysgeusia, a negative CSF viral test does not rule out the diagnosis of meningoencephalitis.

Acknowledgements Cases 1 and 2 of Sect. 4.1 and Case 2 of Sect. 4.2 courtesy of:

- E. D’Adda, MD; M.E. Fruguglietti, MD; Neurologist Stroke Unit Cerebrovascular Dept; ASST Crema Hospital
- M. Borghetti MD, G. Benelli MD; Radiology Unit, Cerebrovascular Dept; ASST Crema Hospital
- G. Merli MD, G. Lupi MD, Department of Anesthesia and Critical Care Medicine, ASST Crema Hospital

References

1. Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. N Engl J Med. 1996;334(8):494–500. https://doi.org/10.1056/NEJM199602223340803.

2. Bartynski WS. Posterior reversible encephalopathy syndrome, part 1 and 2: fundamental imaging and clinical features. AJNR Am J Neuroradiol. 2008;29:1036–42. https://doi.org/10.3174/ajnr.A0928.

3. Bakshi R, Bates VE, Mechtler LL, et al. Occipital lobe seizures as the major clinical manifestation of reversible posterior leukoencephalopathy syndrome: magnetic resonance imaging findings. Epilepsia. 1998;39(3):295–9. https://doi.org/10.1111/j.1528-1157.1998.tb01376.x.
4. Fugate JE, Claassen DO, Cloft HJ, et al. Posterior reversible encephalopathy syndrome: associated clinical and radiologic findings. Mayo Clin Proc. 2010;85(5):427–32. https://doi.org/10.4065/mcp.2009.0590.

5. Miller TR, Shivashankar R, Mossa-Basha M, et al. Reversible cerebral vasoconstriction syndrome, part 1: epidemiology, pathogenesis, and clinical course. AJNR Am J Neuroradiol. 2015;36:1392–9. https://doi.org/10.3174/ajnr.A4214.

6. Schwartz RB, Jones KM, Kalina P, et al. Hypertensive encephalopathy: findings on CT, MR imaging, and SPECT imaging in 14 cases. AJR Am J Roentgenol. 1992;159:379–83. https://doi.org/10.2214/ajr.159.2.1632361.

7. Calabrese LH, Dodick DW, Schwedt TJ, et al. Narrative review: reversible cerebral vasoconstriction syndromes. Ann Intern Med. 2007;146:34–44. https://doi.org/10.7326/0003-4819-146-1-200701020-00007.

8. Chen SP, Fuh JL, Wang SJ, et al. Magnetic resonance angiography in reversible cerebral vasoconstriction syndromes. Mayo Clin Proc. 2010;85(5):1417–9. https://doi.org/10.1016/j.mcp.2009.0590.

9. Aird WC. The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. Blood. 2003;101:3765–77. https://doi.org/10.1182/blood-2002-06-1887.

10. Bartynski WS, Tan HP, Boardman JF, et al. Posterior reversible encephalopathy syndrome after solid organ transplantation. AJNR Am J Neuroradiol. 2008;29:924–30. https://doi.org/10.3174/ajnr.A0960.

11. Gupta S, Kaplan MJ. Pathogenesis of systemic lupus erythematosus. Rheumatology. 7th ed. Philadelphia, PA: Elsevier; 2019. p. 1154–9.

12. Loscalzo J. Endothelial injury, vasoconstriction, and its prevention. Tex Heart Inst J. 1995;22:180–4. https://doi.org/10.1093/brain/awaa239.

13. Sandoo A, van Zanten JJ, Metisso GS, et al. The endothelium and its role in regulating vascular tone. Open Cardiovasc Med J. 2010;4:302–12. https://doi.org/10.2174/18749241004010302.

14. Franceschi AM, Ahmed O, Giliberto L, et al. Hemorrhagic posterior reversible encephalopathy syndrome as a manifestation of COVID-19 infection. AJNR Am J Neuroradiol. 2020;41(7):1173–6. https://doi.org/10.3174/ajnr.A6595.

15. Hernández-Fernández F, Valencia HS, Barbella-Aponte RA, et al. Cerebrovascular disease in patients with COVID-19: neuroimaging, histological and clinical description. Brain. 2020;143:3089. https://doi.org/10.1093/brain/awaa239.

16. Filatov A, Sharma P, Hindi F, et al. Neurological complications of coronavirus (COVID-19): encephalopathy. Cureus. 2020;12:e7352. https://doi.org/10.7759/cureus.7352.

17. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395:1033–4. https://doi.org/10.1016/S0140-6736(20)30628-0.

18. Eltzschig HK, Carmeli et P. Hypoxia and inflammation. N Engl J Med. 2011;364:656–65. https://doi.org/10.1056/NEJMra0910283.

19. Bartels K, Grenz A, Eltzschig HK. Hypoxia and inflammation are two sides of the same coin. Proc Natl Acad Sci U S A. 2013;110:18351–2. https://doi.org/10.1073/pnas.1318345110.

20. Rosa Junior M, Borges EI, Fonseca APA, et al. Hemorrhagic posterior reversible encephalopathy syndrome as a manifestation of COVID-19 infection. Neurology. 2020;94(e11):e116937. https://doi.org/10.1212/WNLI.0000120668.73677.5f.

21. Cross SN, Ratner E, Rutherford TJ, et al. Bevacizumab-mediated interference with VEGF signalling is sufficient to induce a preeclampsia-like syndrome in nonpregnant women. Rev Obstet Gynecol. 2012;5:2–8.

22. McKinney AM, Short J, Truwit CL, et al. Posterior reversible encephalopathy syndrome: incidence of atypical regions of involvement and imaging findings. AJNR Am J Neuroradiol. 2007;189:904–12. https://doi.org/10.3224/ajr.10214/AJR.07.2024.

23. Levitt M, Zampolin R, Burns J, et al. Posterior reversible encephalopathy syndrome and reversible cerebral vasoconstriction syndrome. Distinct Clinical Entities with Overlapping Pathophysiology. Radiol Clin N Am. 2019;57:1133–46. https://doi.org/10.1016/j.rcl.2019.07.001.

24. Covarrubias DJ, Luetmer PH, Campeau NG. Posterior reversible encephalopathy syndrome: prognostic utility of quantitative diffusion-weighted MR images. AJNR Am J Neuroradiol. 2002;23:1038–4.

25. Eichler FS, Wang P, Wityk RJ, et al. Diffuse metabolic abnormalities in reversible posterior leukoencephalopathy syndrome. AJNR Am J Neuroradiol. 2002;23(5):833–7.

26. Hefzy HM, Bartynski WS, Boardman JF, et al. Hemorrhage in posterior reversible encephalopathy syndrome: imaging and clinical features. AJNR Am J Neuroradiol. 2009;30(7):1371–9. https://doi.org/10.3174/ajnr.A1588.

27. Cruz-Flores S, de Assis Aquino Gondim F, Leira EC. Brainstem involvement in hypertensive encephalopathy: clinical and radiological findings. Neurology. 2004;62(8):1417–9. https://doi.org/10.1212/01.wnl.0000120668.73777.5f.

28. Pilato F, Distefano M, Calandrelli R. Posterior reversible encephalopathy syndrome and reversible cerebral vasoconstriction syndrome: clinical and radiological considerations. Front Neurol. 2020;11:34. https://doi.org/10.3389/fneur.2020.00034.

29. Muttilkakal TJ, Wintermark M. MRI patterns of global hypoxic-ischemic injury in adults. J Neuroradiol. 2013;40:164–71. https://doi.org/10.1016/j.neurad.2012.08.002.

30. Wijdicks EF, Campeau NG, Miller GM. MR imaging in comatose survivors of cardiac resus-
4 Posterior Reversible Encephalopathy Syndrome (PRES) and Meningo-Encephalitis in COVID

---

41. Egdell R, Egdell D, Solomon T. Herpes simplex virus encephalitis. BMJ. 2012;344:e3630. https://doi.org/10.1136/bmj.e3630.

42. Steiner I, Budka H, Chaudhuri A, et al. Viral meningoencephalitis: a review of diagnostic methods and guidelines for management. Eur J Neurol. 2010;17(8):999–e57. https://doi.org/10.1111/j.1468-1331.2010.02970.x.

43. Gupta RK, Soni N, Kumar S, et al. Imaging of central nervous system viral diseases. J Magn Reson Imaging. 2012;35(3):477–91. https://doi.org/10.1002/jmri.22830.

44. Finkenstaedt M, Szudra A, Zerr I, et al. MR imaging of Creutzfeldt-Jakob disease. Radiology. 1996;199(3):793–8. https://doi.org/10.1148/radiology.199.3.8638007.

45. Becker JT, Maruca V, Kingsley LA, et al. Multicenter AIDS Cohort Study. Factors affecting brain structure in men with HIV disease in the post-HAART era. Neuroradiology. 2011;54(2):113–21. https://doi.org/10.1007/s00234-011-0854-4.

46. Shah R, Bag AK, Chapman PR, et al. Imaging manifestations of progressive multifocal leukoencephalopathy. Clin Radiol. 2010;65(6):431–9. https://doi.org/10.1016/j.crad.2010.03.001.

47. Misra UK, Kalita J, Phadke RV, et al. Usefulness of various MRI sequences in the diagnosis of viral encephalitis. Acta Trop. 2010;116(3):206–11. https://doi.org/10.1016/j.actatropica.2010.08.007.

48. Molimard J, Baudou E, Mengelle C, et al. Coxsackie B3-induced rhombencephalitis. Arch Pediatri. 2019;26(4):247–8. https://doi.org/10.1016/j.arcped.2019.02.013.

49. Asadi-Pooya AA, Simani L. Central nervous system manifestations of COVID-19: a systematic review. J Neurol Sci. 2020;413:116832. https://doi.org/10.1016/j.jns.2020.116832.

50. Hernandez-Fernandez F, Valencia HS, Barbella-Aponte RA, et al. Cerebrovascular disease in patients with COVID-19: neuroimaging, histological and clinical description. Brain. 2020;143:3089. https://doi.org/10.1093/brain/awaa239.

51. Mahammedi A, Saba L, Vagal A, et al. Imaging in neurological disease of hospitalized COVID-19 patients: an Italian multicenter retrospective observational study. Radiology. 2020;297:E270. https://doi.org/10.1148/radiol.2020201933.

52. Merkler AE, Parikh NS, Mir S, et al. Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) vs patients with influenza. Jama Neurol. 2020;77:1. https://doi.org/10.1001/jamaneurol.2020.2730.

53. Garg RK, Paliwal VK, Gupta A. Encephalopathy in patients with COVID-19: a review. J Med Virol. 2020:1–17. https://doi.org/10.1002/jmv.26207.

54. Baig AM, Khaleeq A, Ali U, et al. Evidence of the COVID-19 virus targeting the CNS; tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci. 2020;11(7):995–8. https://doi.org/10.1021/acschemneuro.0c00174.

55. Moriguchi T, Harii N, Goto J, et al. A first case of meningoencephalitis associated with SARS-CoV-2. Int J Infect Dis. 2020;94:55–8. https://doi.org/10.1016/j.ijid.2020.03.062.

56. Russell B, Moss C, Rigg A, et al. Anosmia and ageusia are emerging as symptoms in patients with...
COVID-19: what does the current evidence say? Ecancermedicalscience. 2020;14:ed98. https://doi.org/10.3332/ecancer.2020.ed98.

57. Hamming I, Timens W, Bulthuis M, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203:631–7. https://doi.org/10.1002/path.1570.

58. Tai W, He L, Zhang X, et al. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. Cell Mol Immunol. 2020;17:613–20. https://doi.org/10.1038/s41423-020-04004-0.

59. Lau SK, Woo PC, Yip CC, et al. Coronavirus HKU1 and other coronaviruses infections in Hong Kong. J Clin Microbiol. 2006;44(6):2063–71. https://doi.org/10.1128/JCM.02614-05.

60. MacNamara KC, Chua MM, Phillips JJ, et al. Contributions of the viral genetic background and a single amino acid substitution in an immunodominant CD8+ T-cell epitope to murine coronavirus neurovirulence. J Virol. 2005;79(14):9108–18. https://doi.org/10.1128/JVI.79.14.9108-9118.2005.

61. Mehta P, McCauley DF, Brown M, et al. HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033–4. https://doi.org/10.1016/S0140-6736(20)30628-0.

62. Al-Olama M, Rashid A, Garozzo D. COVID-19-associated meningoencephalitis complicated with intracranial hemorrhage: a case report. Acta Neurochir. 2020;162(7):1495–9. https://doi.org/10.1007/s00701-020-04402-w.

63. Dogan L, Kaya D, Sarikaya T, et al. Plasmapheresis treatment in COVID-19-related autoimmune meningoencephalitis: case series. Brain Behav Immun. 2020;87:155–8. https://doi.org/10.1016/j.bbi.2020.05.022.

64. Pierchotta V, Chai KL, Valk SJ, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev. 2020;7(7):CD013600. https://doi.org/10.1002/14651858.CD013600.pub2.

65. Zambreanu L, Lightbody S, Bhandari M, et al. A case of limbic encephalitis associated with asymptomatic COVID-19 infection. J Neurol Neurosurg Psychiatry. 2020;91:1229. https://doi.org/10.1136/jnnp-2020-323839.

66. Varatharaj A, Thomas N, Ellul MA, et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. Lancet Psychiatry. 2020;7(10):875–82. https://doi.org/10.1016/S2215-0366(20)30287-X.

67. Xiong W, Mu J, Guo J, et al. New onset neurologic events in people with COVID-19 in 3 regions in China. Neurology. 2020;95(11):e1479–87. https://doi.org/10.1212/WNL.0000000000010034.

68. Pons-Escoda A, Naval-Baudín P, Majós C, et al. Neurologic Involvement in COVID-19: cause or coincidence? A neuroimaging perspective. AJNR Am J Neuroradiol. 2020;41(8):1365–9. https://doi.org/10.3174/ajnr.A6627.

69. Chourgar L, Shor N, Weiss N, et al. CoCo Neurosciences study group. Retrospective observational study of brain magnetic resonance imaging findings in patients with acute SARS-CoV-2 infection and neurological manifestations. Radiology. 2020;297:E313. https://doi.org/10.1148/radiol.2020202422.

70. Montalvan V, Lee J, Bueso T, et al. Neurological manifestations of COVID-19 and other coronavirus infections: a systematic review. Clin Neurol Neurosurg. 2020;194:105921. https://doi.org/10.1016/j.clineuro.2020.105921.

71. Guilment A, Maldonado Slootjes S, et al. Immune-mediated neurological syndromes in SARS-CoV-2-infected patients. J Neurol. 2020;1–7. https://doi.org/10.1007/s00415-020-10108-x.

72. Toscano G, Palmerini F, Ravaglia S, et al. Guillain-Barré syndrome associated with SARS-CoV-2. N Engl J Med. 2020;382(26):2574–6. https://doi.org/10.1056/NEJMc2009191.

73. Gutiérrez-Ortiz C, Méndez-Guerrero A, Rodrigo-Rey S, et al. Miller Fisher syndrome and polyneuritis cranialis in COVID-19. Neurology. 2020;95(5):e601–5. https://doi.org/10.1212/NWNL.0000000000009619.

74. Pilotto A, Odolini S, Masicchio S, et al. Steroid-responsive encephalitis in coronavirus disease 2019. Ann Neurol. 2020;88:423. https://doi.org/10.1002/ana.25783.

75. Scullen T, Keen J, Mathkour M, et al. Coronavirus 2019 (COVID-19)-associated encephalopathies and cerebrovascular disease: the New Orleans experience. World Neurosurg. 2020;141:e437–46. https://doi.org/10.1016/j.wneu.2020.05.192.

76. Zuhorn F, Omaimen H, Ruprecht B, et al. Parainfectious encephalitis in COVID-19: “The Claustrum Sign”. J Neurol. 2020;1–4. https://doi.org/10.1007/s00415-020-10185-y.

77. Yoshikawa K, Kuwahara M, Morikawa M, et al. antibody reactivities and clinical relevance in anti-GQ1b antibody-related diseases. Neurol Neuroimmunol Neuroinflamm. 2018;5(6):e501. https://doi.org/10.1212/NXI.0000000000000501.

78. Chi MS, Ng SH, Chan LY. Asymmetric acute motor axonal neuropathy with unilateral tongue swelling mimicking stroke. Neurologist. 2016;22(6):106–8. https://doi.org/10.1097/NXI.0000000000000102.

79. Hayashi M, Sahashi Y, Baba Y, et al. COVID-19-associated mild encephalitis/encephalopathy with a reversible splenial lesion. J Neurol Sci. 2020;415:116941. https://doi.org/10.1016/j.jns.2020.116941.

80. Wong PF, Craik S, Newman P, et al. Lessons of the month 1: a case of rhombencephalitis as a rare
complication of acute COVID-19 infection. Clin Med (Lond). 2020;20(3):293–4. https://doi.org/10.7861/clinmed.2020-0182.

81. Paterson RW, Brown RL, Benjamin L, et al. UCL Queen Square National Hospital for Neurology and Neurosurgery COVID-19 Study Group. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain. 2020;143:3104. https://doi.org/10.1093/brain/awaa240.

82. Virhammar J, Kumlien E, Fällmar D, et al. Acute necrotizing encephalopathy with SARS-CoV-2 RNA confirmed in cerebrospinal fluid. Neurology. 2020;95(10):445–9. https://doi.org/10.1212/WNL.0000000000010250.