SARS-CoV-2 associated posterior reversible encephalopathy syndrome (PRES) – a review of 82 cases

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ABSTRACT

Objectives: Severe, acute, respiratory syndrome-coronavirus-2 (SARS-CoV-2) infections can be complicated by central nervous system (CNS) disease. One of the CNS disorders associated with Coronavirus Disease-19 (COVID-19) is posterior reversible encephalopathy syndrome (PRES). This narrative review summarises and discusses previous and recent findings on SARS-CoV-2 associated PRES.

Methods: A literature search was carried out in PubMed and Google Scholar using suitable search terms and reference lists of articles found were searched for further articles.

Results: By the end of February 2023, 82 patients with SARS-CoV-2 associated PRES were recorded. The latency between the onset of COVID-19 and the onset of PRES ranged from 1 day to 70 days. The most common presentations of PRES were mental deterioration (n=47), seizures (n=46) and visual disturbances (n=18). Elevated blood pressure was reported on admission or during hospitalisation in 48 patients. The most common comorbidities were arterial hypertension, diabetes, hyperlipidemia and atherosclerosis. PRES was best diagnosed by multimodal cerebral magnetic resonance imaging (MRI). Complete recovery was reported in 35 patients and partial recovery in 21 patients, while seven patients died.

Conclusions: PRES can be a CNS complication associated with COVID-19. COVID-19 patients with mental dysfunction, seizures or visual disturbances should immediately undergo CNS imaging through multimodal MRI, electroencephalography (EEG) and cerebrospinal fluid (CSF) studies in order not to miss PRES.

KEYWORDS:
Infection, SARS-CoV-2, COVID-19, coronavirus, posterior reversible encephalopathy syndrome

INTRODUCTION

There is increasing evidence that Coronavirus Disease-19 (COVID-19) manifests not only in the lungs but also in several other organs.[1] In addition to the lungs, the extra-pulmonary organ most frequently affected is the central nervous system (CNS).[2] CNS manifestations of COVID-19 are very diverse.[2] One of these CNS disorders associated with COVID-19 is posterior reversible encephalopathy syndrome (PRES).[2] PRES is a rare disorder clinically characterised by headache, visual disturbances, mental changes and seizures.[3] PRES is thought to be a syndrome of impaired autoregulation or endothelial dysfunction leading to preferential posterior circulation hyperperfusion.[4] The symptoms of PRES usually come on quickly and can be serious and life threatening. When treated with antihypertensive drugs or anti-seizure drugs, the symptoms often disappear within days or weeks. PRES occurs in patients with high blood pressure, eclampsia, severe infections, kidney disease and certain autoimmune disorders. It can also occur in patients treated with certain anticancer drugs and immuno-suppressants. PRES is diagnosed on the basis of the clinical presentation and the magnetic resonance imaging (MRI) findings.[4] On MRI, PRES associated lesions are usually located in the occipital areas and present as hyperintensity on diffusion weighted imaging (DWI) and hyperintensity on apparent diffusion coefficient (ADC) maps (vasogenic edema). Vascular irregularities are frequently observed. PRES is also characterised by spontaneous resolution of these lesions within a few days or weeks.[5] PRES can also be accompanied by bleeding (haemorrhagic PRES). Differential diagnoses of PRES include acute demyelinating encephalopathy (ADEM), which reposnds to steroids, immune-encephalitis, viral encephalitis, ischemic stroke, mitochondrial stroke-like lesions, cerebral vasculitis, drug-induced leukoencephalopathy, Wernicke encephalopathy and pontine and extra-pontine myelinolysis. PRES is increasingly recognised as a complication of COVID-19.[3] This narrative review summarises and discusses previous and recent findings on severe, acute, respiratory syndrome- coronavirus-2 (SARS-CoV-2) associated PRES.

METHODOLOGY

A literature search was conducted in the databases PubMed and Google Scholar using the search terms "SARS-CoV-2", "COVID-19" and "coronavirus" combined with "PRES", "posterior reversible encephalopathy syndrome", "arterial hypertension", and "visual impairment". In addition, reference lists of available articles were searched for further suitable references. It included the articles that provided detailed information on patients infected with SARS-CoV-2 who experienced PRES. Articles that were not accessible or only available as an abstract or articles in language other than German, English, French or Spanish were excluded.

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Table I Patients with SARS-CoV-2 associated PRES published as per the end of February 2023

Age	G	LOCOP (d)	Presentation	RR	Comorbidities	SeverityC	Outcome	Reference
90	f	21	seizure, CI	227/95	DM, AHT, DVT, PE, AFLU	severe	CR after4 months	[13]
36-70	4f, 4m	1-70	seizure, CI	nr	DM, AHT, HLP, RI, ASKL LTX, DVT, OSA, OB	severe	CR (3), dead (1)	[11]
46	m	nr	seizure, CI	160/90	SM, AHT, OB	severe, MV	CR	[14]
70	m	10	confusion	124/72	Asthma, AHT, ASKL	severe, MV	death	[8]
10	m	nr	seizure	109/70	none	severe,	CR	[15]
48	m	18	MD	180/90	OB	severe, MV	PR	[16]
67	f	nr	MD	178/83	AHT, DM, HU ASKL, asthma	severe, MV	PR	[16]
74	m	15	seizure	150/nr	myeloma	moderate	PR	[17]
67	f	25	MD	193/97	AHT, OB, DM	severe, MV	PR	[18]
58	m	24	MD	189/122	HLP, AHT	severe, MV	CR	[18]
64	f	35	MD, vision ↓	nr	AHT, HU, HLP, AFIB, OSA	severe, MV	CR	[19]
63	f	37	seizure	nr	AHT	severe, MV	CR	[20]
27	f	nr	MD	nr	none	severe	death	[10]
74	f	nr	confusion, agitation, MW	237/nr	HLP, DM, HOT	severe, MV	PR	[21]
64	m	nr	confusion, NCSE	184/nr	nr	severe, MV	PR	[21]
73	m	nr	confusion, seizure	212/nr	nr	severe, MV	CR	[21]
65	f	nr	MD	190/nr	AHT, DM	severe, MV	PR	[21]
69	f	nr	seizure, delirium, mutism	200/116	ASKL	mild	PR	[22]
24	f	nr	delirium, confusion, MW	nr	none	severe, MV	PR	[23]
35	f	0	seizure, blindness	nr	HOT	asymptomatic	nr	[24]
33	f	nr	hallucinations, palinopsy	nr	none	mild	CR	[25]
46	m	13	MD, agitation, MW	130/70	AHT, DM	severe, MV	PR	[26]
66	f	10	MD, seizure	160/nr	nr	severe; MV	death	[9]
59	m	12	confusion	173/96	nonw	severe, MV	death	[12]
64	m	30	seizure, NCSS, MW	nr	nr	severe, MV	CR	[27]
55	m	nr	seizure, anopia, MW	nr	nr	severe, MV	PR	[27]
63	f	nr	seizure, impaired vision	nr	nr	severe, MV	CR	[27]
68	m	nr	MW, impaired vision	nr	nr	severe, MV	PR	[27]
64	f	35	MD, impaired vision	nr	nr	severe, MV	CR	[27]
57	f	9	seizure, MW, aphasia	nr	nr	severe, MV	PR	[27]
61	f	nr	MD, seizure	187/98	none	severe, MV	PR	[28]
52	f	34	seizures	180/97	HIV, RI	severe, MV	PR	[28]
25	f	1	seizure, headache	190/120	none	mild	PR	[29]
54	f	31	seizure, aphasia, anopia	125/78	none	severe, MV	PR	[30]
55	m	7	confusion, lethargy	171/85	AHT, OB, RI, SM, OSA, HLP	mild	CR	[31]
85	m	nr	MD	184/96	AHT, DM, AFIB, RI	asymptomatic	CR	[32]
43	f	1	seizure, lethargy	nr	sickle cell disease, epilepsy	nr	CR	[33]
69	f	17	seizure, halluzinations	180/90	AHT, HLP	severe, MV	PR	[34]
55	f	13	MW, anopia, seizure	178/88	AHT, DM	severe, MV	nr	[34]
65	m	39	seizure	140/100	AHT, DM, pyoderma	severe, MV	CR	[34]
9	m	8	seizures, vomiting	143/92	none	mild	CR	[35]
66	m	16	seizure, IC	nr	AHT, HLP	severe, MV	CR	[36]
64	m	14	IC	170/100	AHT, HLP	severe, MV	CR	[36]
54	f	nr	aphasia, acalculia, FAS, CB	nr	none	mild	PR	[37]
9	m	21	seizure, hallucinations, MD	79/55	none	severe, MV	PR	[38]
30	m	nr	seizure, MD, hemorrhage	nr	none	severe, MV	death of COVID	[39]
nr	f	nr	seizure, headache, lethargy	nr	lupus on cyclophosphamide	asymptomatic	CR	[40]

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Table I Patients with SARS-CoV-2 associated PRES published as per the end of February 2023

Age	G	LOCOP (d)	Presentation	RR	Comorbidities	SeverityC	Outcome	Reference
38	m	14	seizure, aphasia, CB, CI, IC	130/80	steatosis, alcoholism	severe	CR	[41]
62	f	41	seizure	nr	AHT, OB	severe, MV	CR	[42]
5	f	5	seizure, CB	RR ↑	none	severe	CR	[43]
33	f	8	headache, MD, CB	nr	gestational DM, migraine, HOTsevere	CR	[44]	
61	f	24	seizure	nr	nr	severe, MV	CR	[45]
64	f	nr	drowsiness, impaired vision	nr	nr	nr	nr	[46]
74	f	5	confusion, CB, disorientation	170/100	AHT, HLP, AFIB	severe	nr	[47]
nr	nr (n=4)	nr	nr	nr	nr	nr	nr	[48]
90s	f	3	seizure, confusion, hemiplegia	131/63	AHT	severe	nr	[49]
nr	nr	nr	altered mental state	nr	nr	severe, MV	nr	[50]
nr	nr	nr	altered mental state	nr	nr	severe, MV	nr	[50]
54	m	nr	nr	nr	nr	nr	nr	[7]
38	m	10	confusion, agitation, CB	130/80	none	severe	CR	[51]
38	f	3	seizure, confusion, anopia	nr	none	moderate	PR	[52]
nr	nr	nr	nr	nr	AHT	nr	CR	[53]
48	m	nr	disorientation	nr	nr	moderate	nr	[54]
7	f	nr	seizure, CB	nr	none	mild	nr	[55]
8	m	37	MD, nystagmus, seizure	nr	metastatic medulloblastoma	mild, MV	death	[56]
52	f	7	impaired vision	146/72	nr	severe, MV	CR	[57]
9	f	10	seizure, IC	RR ↑	none	moderate	CR	[58]
78	f	nr	delirium	nr	AHT, rheumatoid arthritis	severe	nr	[59]
66	f	nr	CB, confusion, disorientation	nr	AHT, DM, 10 asthma	severe, MV	CR	[60]
39	f	11	MD, IC, seizure	nr	LTX on cyclosporine, MM	severe	CR	[61]
34	f	nr	seizure, confusion	210/110	primigravida	asymptomatic	CR	[62]
67	f	nr	seizure, disorientation	150/88	ASKL	severe	CR	[63]

AFLU: Atrial flutter, AHT: Arterial hypertension, ASKL: Atherosclerosis, CB: Cortical blindness, CI: Cognitive impairment, CR: Complete recovery, d: Days, DM: Diabetes mellitus, DVT: Deep vein thrombosis, FAS: Foreign accent syndrome, G: Gender, HLP: Hyperlipidemia, HOT: hypothyroidism, HU: Hyperuricemia, IC: Impaired consciousness, LOCOP: Latency between onset of COVID-19 and onset of PRES (days), LTX: Liver transplantation, MD: Mental deterioration, MM: Mycophenolate mofetil, MV: Mechanical ventilation, MW: Muscle weakness, NCSE: Non-convulsive status epilepticus, NR: Not reported, OB: Obesity, OSA: Obstructive sleep apnoea, PE: Pulmonary embolism, PR: Partial recovery, severity: Severity of COVID-19, RI: Renal insufficiency, RR: Blood pressure at onset of neurological manifestations or on admission, SM: Smoking

RESULTS

A total of 56 articles were identified, reporting a total of 82 patients with SARS-CoV-2 associated PRES (Table I).[8-63] Ages were reported for 74 patients and ranged from 5 to 90 years. Gender was specified for 75 patients and was 34 male and 41 female. The male to female ratio was 1:1.2. Some of the trapped females were pregnant without suffering from eclampsia. PRES has been reported much more frequently in adults than in children and adolescents. Only five of the included patients were paediatric patients (Table I). The latency between the onset of COVID-19 and the onset of PRES was reported in 48 patients and ranged from 1 day to 70 days (Table I). In nine patients the latency was > 30 days. Blood pressure at admission or highest blood pressure during hospitalisation was reported in 48 patients and was elevated > 125/85 mmHg in 28 patients (Table I). A total of 24 patients had a history of arterial hypertension, 12 had a history of diabetes/gestational diabetes and 10 had hyperlipidemia (Table I). Five had atherosclerosis and three hypothyroidism (Table I).

Clinical presentation of PRES was reported in 76 patients. The most common presentations of PRES were mental deterioration (n=47) seizures or non-convulsive status epilepticus (n=46) and visual impairment (n=18). Nine patients were reported to have muscular weakness, six patients were described with impaired consciousness. Aphasia was reported in four patients and three patients developed delirium (Table I). Hallucinations were reported in three patients (Table I). The clinical presentation of SARS-CoV-2 associated PRES did not differ from non-SARS-CoV-2 associated PRES. PRES was best diagnosed by multimodal cerebral MRI. Few patients had cerebral CT without MRI.[49,53,63] MRI most commonly showed bilateral cortical and subcortical T2/FLAIR hyperintensities in the occipital region. The frontal and parietal regions, but also the basal ganglia and the cerebellum were less frequently affected.[41-63] On multimodal MRI these lesions most commonly presented as vasogenic oedema. Cytotoxic oedema and haemorrhage were rarely observed.[40] Six patients presented with haemorrhagic PRES on imaging.[16,39,48,54,56] Electroencephalography (EEG) was rarely reported and was either normal or showed only diffuse slowing without epileptiform discharges.[41] Cerebrospinal fluid (CSF) studies were rarely performed and were either normal or showed slightly elevated protein.[41]

The severity of COVID-19 was reported in 74 patients. The severity of COVID-19 was classified as "severe" in 58 cases, 39 of which required mechanical ventilation. Four patients were asymptomatic, eight had mild COVID infection, and four had moderate COVID-19 (Table I). The outcome was reported in 63 patients. Full recovery was achieved in 35 patients and partial recovery in 21 patients, while seven patients died (Table I). Regarding the cause of death in seven of the included patients, two patients died from sepsis with multi-organ failure[8,9], one from cardiopulmonary arrest,[10] two patients from respiratory failure,[12,39] one from severe intracerebral bleeding[56] and one with status epilepticus.[11] According to these data, only one patient died as a result of PRES.[11] In none of these cases was an autopsy reported.

DISCUSSION

This review shows that SARS-CoV-2 infections can be complicated by PRES. Morphology, clinical presentation, course and outcome of SARS-CoV-2 associated PRES do not differ from PRES due to other causes. There is a slight excess in females. Although all the age groups can be affected, predominantly adults are affected. Mental deterioration, seizures and visual disturbances are the most common presentations of SARS-CoV-2 associated PRES. SARS-CoV-2 associated PRES particularly occurs in patients with severe COVID-19 and most patients recover either fully or incompletely. No specific risk factors that predispose to the development of PRES could be identified. However, possible contributing factors that could favour the development of SARS-CoV-2 related PRES include arterial hypertension, diabetes and hyperlipidaemia.

The reason why PRES develops in COVID-19 patients is unclear, but it can be speculated that it may be due to severe arterial hypertension, endothelial damage resulting from immune system activation, impaired vascular autoregulation or blood–brain barrier dysfunction.[3] The inflammatory storm has been suggested to pathophysiologically injure the endothelium, resulting in endothelial dysfunction, interstitial fluid extravasation and cerebral oedema, however, PRES is not usually associated with an increase in brain volume.[7] Since COVID-19 is accompanied by a strong immunologic response, immune endotheliopathy is the most likely explanation.[7] The immune hypothesis is supported by the fact that PRES occurs frequently in patients taking immunomodulatory medication and in patients with increased systemic inflammation, such as in autoimmune disease, sepsis, or organ transplants and that it has been reported in association with other immunologic disorders.[64] Impaired autoregulation can also be triggered by renal failure, preeclampsia, or eclampsia, autoimmune disease or immunosuppression.[4] Given the reported slightly higher rates of haemorrhagic PRES in COVID-19 patients,[6] it can be speculated that COVID-19 patients with PRES develop higher blood pressure, a more severe vasculopathy or damage of the blood–brain barrier, or more commonly coagulopathy than patients with PRES due to other causes.

Regarding the short interval between the onset of COVID-19 and the onset of PRES in some patients, it can be speculated that infection with SARS-CoV-2 occurred much earlier than a day before (incubation time 4-14 days) and that it was either asymptomatic or was only mildly symptomatic and therefore went undetected for several days. It is also conceivable that the virus entered the body and triggered the immune response days before the clinical manifestations of COVID-19 and PRES appeared almost simultaneously.

Limitations of the review are that it had a narrative design and therefore some published cases of SARS-CoV-2 associated PRES may have been missed and that data were not analysed statistically. Another limitation is that the data provided in several publications are often reported incompletely and therefore contribute to the pile of "missing data". An article was not added due to concerns from the Cureus editor. Another case was not included because he also had Miller-Fisher syndrome. In nine cases, the latency between the onset

of COVID-19 and the onset of neurological manifestations was > 30 days, making a causal relationship unlikely.

CONCLUSION

This review demonstrates that posterior reversible encephalopathy syndrome (PRES) can be a central nervous system (CNS) complication of COVID-19 and that patients with COVID-19 plus mental dysfunction, seizures or visual impairment should undergo immediate CNS imaging, electroencephalography (EEG) and cerebrospinal fluid (CSF) studies. Because patients with severe COVID-19 develop PRES particularly during hospitalisation in an intensive care unit (ICU), it can be easily missed when patients are not awake or not undergoing prospective cerebral imaging. Although the prognosis of PRES is good in most cases, neurologists must remain vigilant that SARS-CoV-2 infections can be complicated by PRES and that these patients require immediate evaluation and treatment to improve their outcome.

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