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REVIEW ARTICLE

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Neurological Manifestations of COVID-19: A systematic review and current update

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The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in December of 2019 in the city of Wuhan, China. Since the outbreak, various reports detail its symptoms and outcomes, primarily focusing on respiratory complications. However, reports are emerging of the virus' effects systemically, including that of the nervous system. A review of all current published literature was conducted, and we report that headache and anosmia were common neurological manifestations of SARS-CoV-2. Less common symptoms include seizure, stroke and isolated cases of Guillain-Barre syndrome. Further research is now warranted to precisely determine the relationship between those patients developing neurological sequelae, their clinical state and any subsequent morbidity and mortality.

KEYWORDS
COVID-19, nervous system, neurology, SARS-CoV-2

1 | INTRODUCTION

Coronaviruses, such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), are pathogens that largely affect and subsequently cause symptoms of the respiratory system. An outbreak in the city of Wuhan in December of 2019 saw the introduction of a new coronavirus strain, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) in February 2020. This novel virus, which has consequently sparked a global pandemic, has also been widely reported to display a range of respiratory manifestations. Milder, and most commonly, symptoms include fever, fatigue and cough; however, more severe cases of the disease can induce respiratory distress, renal and cardiac failure and eventually death.[1]

In addition to respiratory symptoms, reports are emerging of neurological manifestations of SARS-CoV-2, which range from milder presentations such as headache to severe complications such as seizures and strokes. We provide a comprehensive review of the neurological manifestations of SARS-CoV-2 and its outcomes on mortality and propose the implications this has on clinical practice now and in the future.

1.1 | Literature search strategy

A comprehensive electronic literature search was done on PubMed, SCOPUS, Embase, Cochrane database, Google Scholar and Ovid in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines to identify the articles that discussed the neurological presentations and relation with COVID-19. Keywords used were "Neurology" "COVID-19" "SARS-CoV2" "Neurological manifestations" "Nervous system" "Guillain-Barre syndrome" "Neuropathy" "Outcomes" "Stroke" "Nerve" "Critical care". The search terms were used as keywords and in combination as MeSH terms to maximize the output from literature findings. A staged literature search was done, whereby a separate literature search was performed for each section within this article and all the relevant studies were identified and summarized separately. If a paper is reporting on many aspects of COVID-19 and neurology

aspect, then the results have been shared between different parts of this review. The relevant articles are cited and referenced within each section separately. No limit placed on publication time or language of the article. All the relevant articles were identified and screened by three authors; the results are summarized in narrative manner in each relevant section within the text of this review. A summary table of each section is provided where appropriate.

Studies were included if they have reported outcomes on any aspects of neurology in relation to COVID-19; the main exclusion criteria were editorials, commentary, narrative reviews with no reports on case outcomes or proposed treatment method. All the studies and data collection were done by two authors (AW and MA), and disagreements were resolved by consensus and involvement of senior author (AH).

2 | RESULTS

PRISMA flow chart is reported as in Figure 1. A total of 339 articles were found; after removal of duplicates and non-original research papers, a total of 38 articles were used for full-text screening; and finally, only 31 studies met the final inclusion criteria and were included in our study. They are summarized in Table 1. Among those studies, there were 13 case reports, 2 observation studies of between 8-382 case-cohort size, 13 retrospective, 2 prospective and 1 cross-sectional study. Among the 31 studies, 7 reported on Guillain-Barre syndrome, 11 reported on headache, 5 reported on olfactory dysfunction, and 5 reported on acute cerebrovascular accidents.

2.1 | Mechanism of neurological pathology

The respiratory manifestations of SARS-CoV-2 are well documented and known. There is an increasing body of significant anecdotal evidence suggesting anosmia as being a symptom of SARS-CoV-2, giving rise to the possibility that there may be a degree of neurological involvement with the infection.

It has been proposed that SARS-CoV-2 gains entry to the CNS by one of two ways: firstly, by systemic vascular dissemination and, secondly, more locally across the cribriform plate of the ethmoid bone, which may or may not have implications regarding the much-reported anosmia that patients with SARS-CoV-2 experience.[2] Baig et al propose that once in the systemic circulation, the virus invades neural tissue due to its properties of neurotropism. Here, it binds to and interacts with angiotensin-converting enzyme 2 (ACE2) receptors in the capillary endothelium.[2]

There is certainly prescience for SARS-CoV-2 possessing such neuroinvasive properties. Like its sister virus SARS-CoV responsible for the outbreak in 2003, SARS-CoV-2 gains entry to cells via ACE2, which it binds via spike proteins.[2] ACE2 has previously been reported to be expressed in the epithelium of the upper and lower

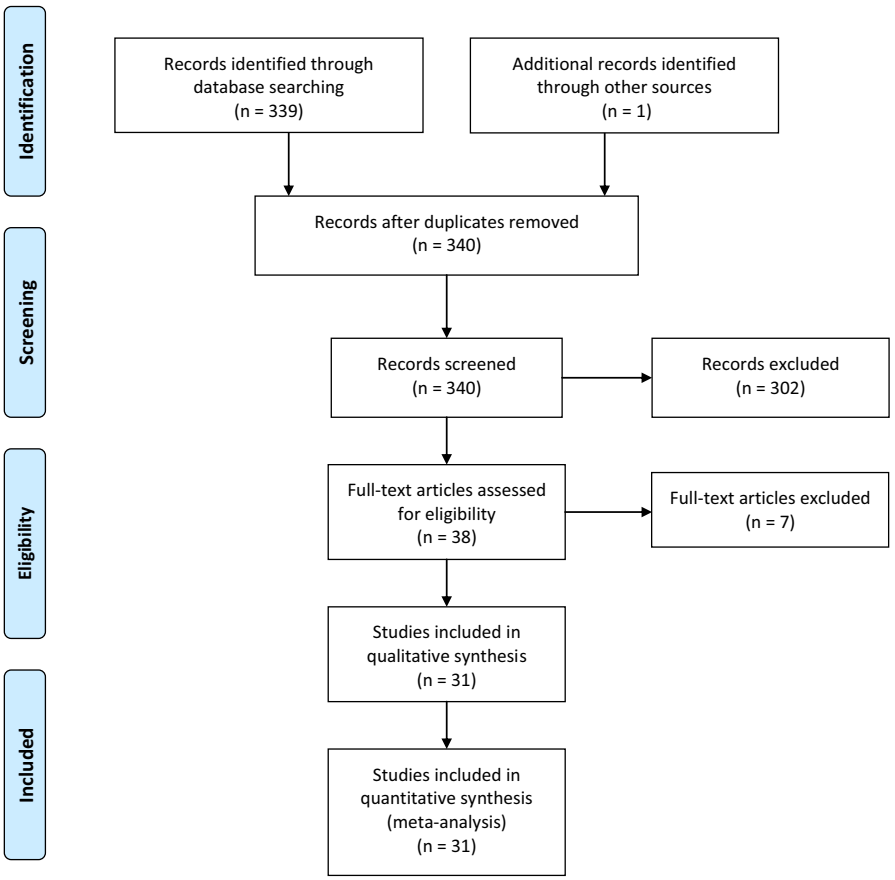

FIGURE 1 PRISMA flow chart for literature search results

TABLE 1 Summary of 31 studies including neurological manifestations of SARS-CoV-2. Author, study type, symptoms and outcomes have all been recorded

Author	Study type	Number of patients	Presenting symptoms	Outcomes
Abdelnour et al[29]	Case report	1	Bilateral lower limb weakness and numbness Hyporeflexia Ataxia Confusion	Spontaneous recovery of power and gait, discharged on day 18 of admission (day 21 of onset)
Alberti et al[14]	Case report	1	Guillain-Barre syndrome	Death (progressive respiratory disease)
Avula et al[30]	Retrospective review	4	Identified 4 patients presenting with an acute stroke + SARS-CoV-2 positive	
Camdessanche et al[17]	Case report	1	Guillain-Barre syndrome	
Chen et al[8]	Retrospective review	99	Confusion (9%) Headache (8%)	
Chen et al[31]	Retrospective study	113	Headache (11%) Dizziness (8%)	
Coen et al[16]	Case report	1	Guillain-Barre syndrome	
Dugue et al[32]	Case report	1	Sustained upwards gaze Bilateral leg stiffening Abnormal EEG	
Duong et al[33]	Case report	1	Headache Confusion Seizure Encephalopathy Disorientation Hallucinations	
Giacomelli et al[34]	Cross-sectional study	59	Olfactory and/or gustatory dysfunction (34%)	
Gilani et al[35]	Retrospective review	8	Anosmia (100%) Gustatory dysfunction (25%)	
Hopkins et al[36]	Observational cohort	382	Anosmia (86%)	Cumulative improvement in anosmia (79%)
Huang et al[37]	Prospective study	41	Headache (8%)	
Kaya et al[38]	Case report	1	Confusion Visual agnosia	
Klok et al[11]	Retrospective review	184	Ischaemic stroke (1.6%)	
Lechien et al[39]	Prospective study	417	Headache (45%) Olfactory dysfunction (86%), 80% of whom were anosmic, with the remaining 20% hyposmic Gustatory dysfunction (89%)	Olfactory dysfunction persisted in 63% of people with clinically resolved infection
Li et al[9]	Retrospective review	221	Acute cerebrovascular accident (6%)	
Lodigiani et al[12]	Retrospective review	338	Ischaemic stroke (2.5%)	

(Continues)

TABLE 1 (Continued)

Author	Study type	Number of patients	Presenting symptoms	Outcomes
Mao et al[7]	Retrospective review	214	Headache (13%) Dizziness (17%) Reduced consciousness (8%) Acute cerebrovascular accident (3%) Ataxia (0.5%) Seizure (0.5%) Olfactory dysfunction (5%) Gustatory dysfunction (6%)	
McAbee et al[40]	Case report	1	Status epilepticus Encephalitis	
Moriguchi et al[41]	Case report	1	Headache Loss of consciousness Seizure Encephalitis	Impaired consciousness at day 15
Oxley et al[10]	Case report	5	Ischaemic stroke	Discharge (60%) Still inpatients (40%)
Sedaghat et al[18]	Case report	1	Guillain-Barre Syndrome	
Sun et al[42]	Observational study	8	Headache (12.5%)	
Toscano et al[15]	Retrospective review	5	Guillain-Barre Syndrome (100%)	
Virani et al[19]	Case report	1	Guillain-Barre Syndrome	
Wan et al[43]	Retrospective review	135	Headache (33%)	
Wang et al[44]	Retrospective review	138	Dizziness (9%) Headache (7%)	
Wang et al[45]	Retrospective review	69	Headache (14%) Dizziness (7%)	Hospitalization (66%) Discharge (27%) Death (8%)
Yang et al[46]	Retrospective review	52	Headache (6%)	
Zhao et al[20]	Case report	1	Guillain-Barre Syndrome	

airways, alongside the capillary endothelium of the central nervous system (CNS).[3] A study conducted into the structural integrity of the SARS-CoV-2 spike glycoprotein, revealed an 10- to 20-fold increase in affinity to ACE2 when compared to the SARS-CoV spike protein.[4] This could be explained by the fact that whilst structurally similar, the two spike glycoproteins are not identical, as identified by a BLASTp search of the two structures.[4] This may also explain why differences in the prevalence of neurological manifestations are being reported between the sister viruses.

Yet, it must be noted that not all human cell lines which express ACE2 are liable to infection with the novel coronavirus. However, despite the paucity of data regarding the neurotropism of SARS-CoV-2, there is an increasing awareness that its neurological manifestations are something to be recognized alongside its more well-understood respiratory presentation.

2.2 | Neurological manifestations

After having conducted a review of all the literature on PubMed pertaining to the neurological manifestation of SARS-CoV-2 using key terms such as "Covid AND neurology"; "Covid AND nervous system", we summarize the findings of 31 such papers that were available to review at the time in Table 1. Key symptoms reported were headache and dysfunction of olfaction and gustatory sensation. However, it is important to note that no papers as of yet have sought to determine whether neurological involvement is a predictor of poor outcomes in patients with SARS-CoV-2, something which we feel may be worthwhile.

It is worth mentioning that all studies in this area to date limit themselves to patients admitted to hospital with SARS-CoV-2. Such a population are more likely to have significant other co-morbidities, and this may influence the rate of neurological sequelae. Studies investigating the incidence of neurological and other extra-respiratory symptoms in patients within the community are called for. Whether neurological manifestations of SARS-CoV-2 are as a direct result of the neuroinvasive properties of the virus or as an indirect consequence of downstream multi-organ dysfunction and aberrant biochemistry is yet to be fully understood, most likely however, is it a combination of both.

2.2.1 | General neurological symptoms

Given the global nature of SARS-CoV-2, the lack of any large-scale observational studies investigating the CNS involvement of the novel coronavirus is surprising. Numerous individual case reports exist which suggests that some patients exhibit neuropsychiatric complications of the virus such as altered consciousness[5] and encephalopathy[6]; however, such reports are limited by their power. Of the limited published research available, most centre in China from the beginning of the SARS-CoV-2 pandemic. An early study from city of Wuhan, China, of 214 hospitalized patients with SARS-CoV-2 reported that over a third (36.4%) of patients had some degree of neurological involvement suggesting that this may be an under-reported and overlooked component of the disease course. They noted that headache and dizziness were the two most reported CNS manifestations at 17% and 13%, respectively. The incidence of more severe neurological sequelae such as cerebrovascular accidents and seizures was low at 3% and 0.5%, respectively. Those with "severe" infections with SARS-CoV-2 were found to be more likely to suffer from neurological complications; however, the authors did not specify the methodology of distinguishing between a severe and non-severe infection with SARS-CoV-2.[7]

Interestingly, they noted that most neurological manifestations occurred early on in the disease which may pose to be an important early predictor of future clinical deterioration. Another similar such retrospective series by Chen et al from the city of Wuhan described that confusion (9%) and headache (8%) were symptoms reported by such patients; importantly however, neurological complaints were significantly less prevalent than the typical respiratory symptoms of cough (82%) and dyspnoea (31%).[8] More significant and potentially long-lasting neurological complications of SARS-CoV-2 were highlighted by Li et al in a study of 221 patients, and 6% developed severe neurological disease: ischaemic stroke, haemorrhage of cerebral vein thrombosis, of which a significant proportion died as a result.[9]

2.2.2 | Stroke

Worryingly, Oxley et al[10] reported five cases of large vessel stroke in patients younger than 50 who had a diagnosis of SARS-CoV-2. The youngest two patients, aged 33 and 37, had no previous medical history. Two further studies detailing the rate of thromboembolic complications in patients with SARS-CoV-2 noted the incidence of ischaemic stroke to be 1.6%[11] and 2.5%,[12] respectively. Both authors recognized that the incidence of thrombotic complications was remarkably high for their particular institutions. There are clearly additional risk factors predisposing patients with SARS-CoV-2 to develop thromboembolic stroke beyond the traditional cardiovascular and metabolic co-morbidities and those pertinent to a protracted stay within intensive care settings.

The thrombo-inflammatory nature that SARS-Cov-2 predisposes patients to, was described by Connor and colleagues who reported the coagulative parameters in 16 critically ill patients.[13] They found that fibrinogen (94%), platelet (62%) and D-dimer (100%) levels were increased, as well as interleukin-6 (IL-6) (100%). They propose a correlation between inflammation and subsequent coagulopathy, by IL-6 and fibrinogen, respectively.[13] Upon damage to the alveoli, an inflammatory state is generated, and as a result, the production of inflammatory cytokines is released, including IL-6.

The downstream effects are broadly categorized into two sequelae: firstly, the production of pro-coagulative factors and, secondly, damage to capillary endothelium resulting in dysregulation of its anti-thrombotic properties. Both of which result in the formation

of microvascular thrombosis, that in turn have the potential to embolize systemically.[13] The pathophysiology of pro-thrombotic states following viral infection has been extensively documented and mirrors the proposed mechanism by Connor et al However, we must also consider the possibility that the predisposition to coagulopathy and thrombotic events may well be explained by the long stays in ITU and consequent immobility.

2.2.3 | Guillain-barre syndrome

There have also been eleven confirmed case reports and another potential report of Guillain-Barre syndrome (GBS) as being a significant neurological sequelae of SARS-CoV-2. Of the eleven cases in published literature, there is considerable variability in the onset of features of GBS and the typical respiratory symptoms of SARS-CoV-2. One paper reported symptoms of GBS at initial presentation to healthcare settings alongside only mild fever,[14] whereas a further nine patients reported symptoms of GBS, five to eleven days post-diagnosis with the novel coronavirus[15-19]Despite the inconsistent onset of symptoms in relation to the diagnosis of COVID-19, it is reassuring that the majority of reports describe consistent clinical features of marked lower limb weakness over upper limb and loss of deep tendon reflexes with variable sensory abnormalities. Interestingly however, raised cerebrospinal fluid protein was not universal in this cohort of patients, and in patients with significant respiratory compromise from SARS-CoV-2, measuring vital capacity due to neuromuscular failure from GBS to further support the diagnosis may not be plausible.

Another report by Zhao et al suggests GBS as a presenting symptom of the novel coronavirus but it is unclear whether this is a true association or merely coincidental.[20] It is well documented that GBS is associated with recent inoculation from a potential range of pathogens, which in itself can explain the clinical heterogenicity of the disease.[21] Several mechanisms by which a virus induces an acute areflexic state in GBS have been proposed. Most likely is that antibodies against surface glycoproteins are produced against a pathogen which also respond to similar native protein structures found of the surface of neurones leading to the clinical features seen in GBS.[19] Other plausible theories include one described by McGonagle et al who describe a "macrophage activation syndrome," also known as cytokine storm, and the subsequent hyperinflammation may also be implicated in the pathogenesis of GBS in patients with SARS-CoV-2.[22]

A clear time lag between infection with the primary causative pathogen and development of neurological sequelae is the classic phenotype of GBS and has been described as the "post-infectious" presentation. However, it is clear that from some case reports, this post-infectious phenotype may not explain why a select number of patients present with either concurrent symptoms of SARS-CoV-2 and neurological involvement or those that present with GBS initially. Zhao et al[20] proposed a so-called "parainfectious" profile pattern whereby GBS occurs at the same time of an acute episode of infection. This may go some way to explain some of the early onset

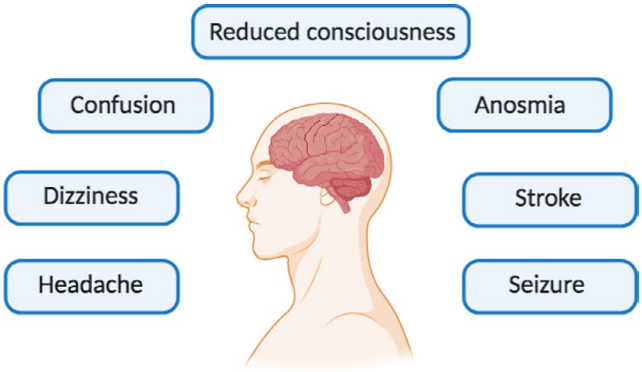

FIGURE 2 Illustration of reported neurological manifestations of SARS-CoV-2

cases of GBS, some of which preceded without significant respiratory involvement and in the absence of a history of any other plausible infection known to cause GBS.

Toscano et al[15] raised an important point in being able to distinguish between GBS and critical illness polyneuropathy, particularly in patients with SARS-CoV-2 who have prolonged admission to intensive care. These consequences of extended intensive care are typically seen later in the course of major illness than GBS but as we have explored, relying on purely time as a differentiator may prove to be difficult.

Historical research has shown that coronaviruses do have the potential to induce demyelinating disease in mice, albeit a central demyelination type picture.[23] There has been an interesting case of GBS overlapping with Bickerstaff's encephalitis documented in the previous MERS-CoV[24] outbreak and a report of a 5-year-old developing GBS after contraction of coronavirus OC43.[25] So, in combination with animal models, previous reports of neurological involvement in sister viruses and current emerging reports, it does seem that GBS is associated with the ongoing SARS-CoV-2 pandemic. But due to so few published reports and the difficulty in proving a direct cause and effect relationship between a single pathogen, it may be complex to explore this further in clinical practice. The neurological symptoms reported by patients are represented in Figure 2.

2.2.4 | Critical illness polyneuropathy/myopathy

The long-stay admissions that some patients are currently experiencing may also pose another issue, that of post-intensive care syndrome (PICS), in particular critical illness polyneuropathy and myopathy (CIPNM). Case reports from SARS-CoV detail patients who experienced CIPNM following infection with the virus.[26] The underlying mechanism, though not fully understood, is thought to be due to systemic inflammatory response syndrome (SIRS) that results.[27] This mediates the release of pro-inflammatory cytokines and free radicals, which affect the microcirculation of both the central and peripheral nervous system by reducing oxygen and nutrient delivery.[27] It is also important to note that risk factors for PICS have

been identified and include long durations of mechanical ventilation, hypoxia and sepsis, features that are common to severe SARS-CoV-2 cases.[27] Yet, no reports detail such symptoms in SARS-CoV-2 patients thus far; however, due to the similarity of the sister viruses, this may be a potential long-term complication.

2.3 | How neurology affects outcomes and mortality

Current published studies have suggested that neurological involvement in the pathogenesis of SARS-CoV-2 does seem to be associated with a more "severe" infection and subsequent mortality. However currently, no direct cause and effect has been attributed to neurological deterioration in patients with SARS-CoV-2 and this relationship could just as plausibly be explained by association with other multi-organ system failures. The direct effect on mortality and morbidity in such "neurological involving" patients is yet to be elucidated.

Interestingly, peripheral nervous system involvement by way of anosmia has been shown to be the initial presentation of SARS-CoV-2 in 36% of patients a recent Spanish case-control study. These so-called smell and taste disorders (STD) were found to be significantly more prevalent in SARS-CoV-2 patients than in influenza patients.[28] This opens the possibility of more prompt isolation of suspected cases and control of the pandemic if the typical symptoms of fever and cough are indeed preceded by anosmia, even if only for a select group of people.

It has been proposed that SARS-CoV-2, like other viruses such as avian influenza and SARS-CoV, can infiltrate the mammalian brainstem via trans-synaptic transfer which can lead to dysfunction of the cardiorespiratory centres of brainstem.[2] It has therefore been suggested that CNS infiltration of SARS-CoV-2 may explain the deterioration of some patient's respiratory effort and their subsequent need for ventilation. Hence, close and serial neurological observations as an adjunct to routine serial observations may prove to be an early warning marker of impending deterioration. This of course needs further study.

2.4 | Implications on clinical practice

Whilst respiratory symptoms of SARS-CoV-2 are well recognized and subsequently protocols are in place to screen for and manage these, scope remains for this to be broadened to cover neurological symptoms of the disease.

As referenced to previously, the first paper to describe neurological involvement in SARS-CoV-2 patients concluded that symptoms were much more common in patients with "severe" forms of the disease, defined by respiratory symptoms.[7] They also reported that typical symptoms, such as cough and lethargy, are less pronounced in severely unwell patients.[7]

The implications this has on current clinical practice are therefore twofold. Firstly, that all patients, but especially those with "severe" SARS-CoV-2, must be monitored for the progression of neurological symptoms, as this may indicate a worsening of their condition. This should also include coagulation parameters, as suggested by Connor's et al due to the predisposition of thrombosis the virus conveys. Secondly, that patients presenting with new-onset focal neurology, with or without the presence of coryzal symptoms, should be reviewed and treated with suspicion of SARS-CoV-2 infection. This will allow the early detection of the disease and therefore prevention of deterioration or transmission.

To fully understanding the impact of SARS-CoV-2 on the nervous system, it is essential that documentation of all neurological symptoms is collected for patients infected with the disease, so that further analysis can be performed into neurological manifestations. An aspect of SARS-CoV-2, not yet fully understood, is the long-term sequelae the virus may have on different systems of the body[47-50]. Again, detailed documentation and long-term follow-up of recovered SARS-CoV-2 patients will allow conclusions to be drawn on this area.

2.5 | Future research

More data are required to establish the prevalence and, importantly, the implications of neurological manifestations in SARS-CoV-2 patients, both short- and long-term, including mortality rates. As more case reports become available, we hope a stronger correlation can be established between the two. Diligent documentation of all neurological symptoms is recommended to help achieve this. The mechanism underlying the neuroinvolvement of SARS-CoV-2 is also yet to be fully understood and remains an area of interest. Identifying modes of transmission is essential in possibly reducing spread and establishing novel therapeutics, to target the virus.

3 | CONCLUSION

The underlying pathophysiology of neurological manifestations in SARS-CoV-2 remains to be fully determined. Increasing numbers of papers are reporting neurological involvement in patients, but more data are required to adequately correlate the two and the impact this has clinically. We recommend close monitoring for neurological symptoms and coagulopathy, and to have a low threshold for patients presenting with new-onset focal neurology, as possible carriers of the disease.

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CONFLICTS OF INTEREST

There are no conflicts of interest or sources of support.

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