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SYSTEMIC REVIEW

Neurological Deficits of Coronavirus Disease-19: A Systematic Literature Review

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ABSTRACT

Aim: To review neurological aspects of patients infected with COVID-19 including neurological dysfunctions and possible pathophysiology.

Methods: A systematic review of articlesfrom PubMed, Ovid MEDLIN, DOAJ databases and grey literature included the WHO-COVID-19 database, and medRxiv.Articles published from January 2020 until June 2020 were included in the review. Out of the226 titles and abstracts, 213 were identified after the removing duplicates. With a screening of 119 studies carried by all authors, 83 full-text articles were assessed based on inclusion criteria of the neurological perspectives with COVID-19. Subsequently, 45 texts were removed. A total of 38 studies were included in the last scrutiny.Specifically, case reports, cohort studies, and case series were included

Results: Reviewed evidence was presented in textual and tabulated format, which includes methodology, characteristics of included studies and summary of findings. Correlational evidence of COVID-19 disease and neurological dysfunctions with possible pathophysiology isreviewed.

Conclusion: The findings provide evidence for physicians and neurologists working with COVID-19 patients about the possible probable complications and clinical presentations due to the SARS-CoV-2 infection.

Keywords: COVID-19; SARS-CoV-2; Coronavirus Disease; Respiratory illness; Neurology; Nervous system; Critical Illness;

INTRODUCTION

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2 or 'novel' coronavirus), which is the pathogenic agent for coronavirus disease (COVID-19) is a beta coronavirus, one of the four genera of coronaviruses. Pneumonia of unfamiliar origin was detected in Wuhan province of China on 31 December 2019. World Health Organization announced this infection as coronavirus disease (2019) COVID-19 on 11 February. COVID-19 has since then spread worldwide [1], and WHO declared it a 'pandemic' on March 11, 2020[2].It has caused 416,614,051confirmed cases and 5,844,097confirmed deaths worldwide as of February17, 2021[3]. The virus spreads through droplets, with an incubation time period of 5 to 14 days and a case fatality rate of 1.8 to 3.4% [4].Patients show pneumonia-like illness with fever, cough, muscle aches and dyspnea, symptoms similar to the SARS-CoV (Severe acute respiratory syndrome-coronavirus) outbreak in 2003. Patients with severe disease have reported neurological dysfunctions. A study comprising 214 patients with COVID-19 from Wuhan, the initial epicentre of the pandemic, revealed that 36.4% patients presented with neurological symptoms, including vertigo (16.8%), headache (13.1%), diminished taste (5.6%), impaired smell (5.1%) and stroke (2.8%)[5]. Patients with neurological symptoms may show no pulmonary symptoms and can maintain normal oxygen blood levels[6]. In some cases, patients can manifest neurological symptoms before showing respiratory or cardiovascular symptoms; however, patients with severe disease are extremelyat risk to develop neurological symptoms[7]. The review aims to address physicians, intensivists and neurologists working with probablepatients of COVID-19 about the possible neurological manifestations and complications.

Neuropathology and immune-mediated injury: SARS-Cov-2 could affect the central nervous system through direct invasion or indirectly through metabolic or immune-mediated mechanisms; Angiotensin-converting-enzyme-2-receptors (ACE-2-receptors) located on the neurons and glial cells are primary site of SARS-CoV-2 attachment, subsequently leading to viral entry, multiplication, and neuronal damage[5].Mice experiments have shown that coronavirus enters the brain within seven days of infection through a retrograde pathway, after attaching on the olfactory epithelium and passing through the cribriform bone[6]. Viremia disrupts the blood-brain barrier, causing direct viral entry. Viral invasion of the nerve terminal provides access to the nervous system through the synapses. Moreover, systemic hypoxia due to viral pneumonia causes hypoxic brain impairment. The contributing factors include anaerobic metabolism, hypercarbia, hypoxia, peripheral vasodilation, and accumulation of toxic compounds. These factors may lead to CNS insult with neuronal distension and cerebral edema which results in neurological manifestations of the coronavirus (2019) disease[5,7]. The damage of the nervous system may be mediated by the immune system. The pathology of severe viral infection is linked to a systemic inflammatory response syndrome (SIRS) through systemic cytokine storm. COVID-19 could be linked to severe pneumonia, and virus-induced SIRS or SIRS-like immune disorders. CoV infections potentially infect astrocytes, microglia, and macrophages in the CNS. The neurotropic virus may induce a pro-inflammatory state. The augmented levels of erythrogenic cytokines, activated T-lymphocytes, macrophages, and endothelial cells lead to immune-mediated injury[8].IL-6 is an imperative member of the cytokine that has a positive correlation to the symptoms of COVID-19 symptoms. IL-6 causes vascular leakage, activation of the coagulation cascade, and end-organ damage[8]. These all result in acute encephalitis with or without strokes.

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MATERIAL AND METHODS

Search strategy: Two independent reviewers searched PubMed, Ovid MEDLINE, DOAJ and the reference lists of articles for inclusion. Grey literature search included the WHO-COVID-19 database, and medRxiv, the preprint server from January 2020, to June 2020.The search strategy used in all databases was Coronavirus, Sars-CoV-2, COVID-19, pathology, neurology. Preferred Reporting Items for Systematic Reviews. The papers that were included were identified as case reports, cohort studies,

case series, reviews associatedwith the neurological findings in COVID-19 patients. The search was limited to papers published in English only. The Preferred Reporting Items for Systematic Reviews (PRISMA) diagram and checklist was utilized for reporting the search findings.After the titles and abstracts of potentially relevant articles were reviewed in the initialstage, full text articles were to be reviewed in the subsequentstage to assess for inclusion eligibility. Any disagreements were resolved by a third reviewer to reach consensus.PRISMA flow sheet for the search strategy is given in Figure 1.Data was extracted as author's name, study design, year of publication, possible pathophysiology and, the relative frequency of neurological dysfunctional findings.

Eligibility Criteria: The following criteria for eligibility was employed for the review. There were no language restrictions for articles published from January 2020 until June 2020. Case reports, Cohort studies, case series, correspondences, brief communications and reviews were added were included.COVID-19 and links to arterial strokes, cerebral venous thrombosis, encephalopathy, delirium, encephalitis, seizures, epilepsy, anosmia, or ageusia were found.Incidence of Acute peripheral neuropathy due to SARS-CoV-2 including Guillain-Barre Syndrome, Miller-Fisher syndrome or polyneuritis cranialis was assessed.

RESULTS

The PRISMA flowchart is attached in figure 1. Our literature search identified 226 abstracts, of which full-text articles were focused on the neurological perspectives of COVID-19. After removing duplicates, 213 articles were identified, with a screening of 119 studies carried by all authors. Subsequently, 45 texts were removed. A total of 38 studies were included in the final review. Detailed characteristics of findings from the review are presented in Table 1. Characteristics of included studies and summary of findings are listed in Table 2.

Fig. 1: PRISMA flowchart

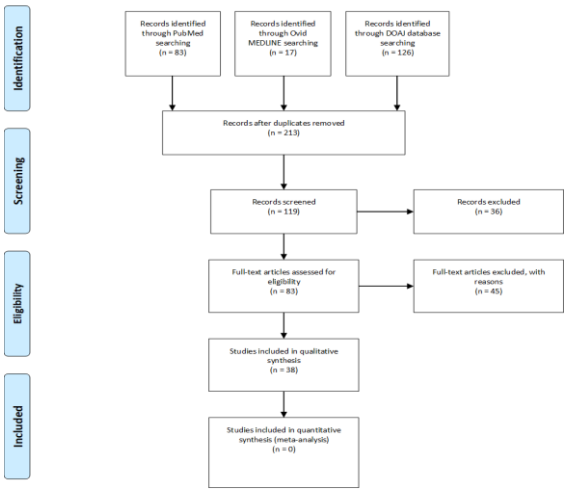

Table 1: Methodology of located studies.

Title of Study	Type of study	Possible pathophysiology	Reference
Focal status epilepticus as unique clinical feature of COVID-19: A case report.	Case report	Viral invasion of neurons and glial cells via ACE-2-receptor binding	(Vollono et al., 2020, p. 110)
COVID-19: ICU delirium management during SARS-CoV-2 pandemic	Review	Metabolic dysfunction	(Kotfis et al., 2020, p. 3)
COVID-19 presenting as stroke	Review	Pneumonia-related cerebral hypoxia	(Avula et al., 2020, p. 116)
A first case of meningitis/encephalitis associated with SARS-Coronavirus-2	Case Report	Viral invasion of neurons and glial cells via ACE-2-receptor binding	(Moriguchi et al., 2020, p. 56)
Guillain Barre syndrome associated with COVID-19 infection: A case report	Report		(Sedaghat & Karimi, 2020, p. 233)
Early Guillain-Barré syndrome in coronavirus disease 2019 (COVID-19): a case report from an Italian COVID-hospital	Case Report		(Ottaviani et al., 2020, p. 1353)
Miller Fisher Syndrome and polyneuritis cranialis in COVID-19	Case Report		(Gutiérrez-Ortiz et al., 2020)
Prevalence and Duration of Acute Loss of Smell or Taste in COVID-19 Patients	Brief Communication	Olfactory nerve invasion and destruction by SARS-CoV-2; Olfactory dysfunction and SARS-CoV-2-induced destruction of the oral cavity's epithelium after binding at the ACE-2-receptor on mucosal cells. This receptor is absent in the olfactory epithelium	(Lee, Min, Lee, & Kim, 2020, p. 5)
Anosmia in COVID-19 patients	Cohort Study		(Hornuss et al., 2020, p. 1)
COVID-19 and stroke—A global World Stroke Organization perspective	Case Report	Thrombotic vascular occlusion due to inflammation-associated hypercoagulability	(Markus & Brainin, 2020, p. 362)
Characteristics of ischemic stroke associated with COVID-19	Letter		(Beyrouti et al., 2020, p. 889)
Intravenous Thrombolysis for Stroke in a COVID-19 Positive Filipino Patient, a Case Report	Case Report		(Co, Yu, Laxamana, & David-Ona, 2020, p. 234)
Neurological manifestations and complications of COVID-19: A literature review	Literature Review	Cytolytic T-cell-mediated dysregulated immune responses & inflammatory cytokines; Infection-induced cardiovascular compromise, cardiac emboli after viral cardiac injury	(Ahmad & Rathore, 2020, p. 11)
Venous cerebral thrombosis in COVID-19 patient	Case Report		(Garaci, Di Giuliano, Picchi, Da Ros, & Floris, 2020, p. 116871)
COVID-19 Presenting with Seizures	Case Report	Retrograde viral movement into the CNS via cranial nerves, hematogenous spread via circulating lymphocytes, cytokine-mediated damage to the blood-brain barrier	(Sohal & Mansur, 2020)

Table 2: Characteristics of included studies and summary of findings.

Author Name	Publication Year	Number of patients with neurological dysfunction	Finding	%age
Lee et al. Hornuss et al. Ahmad et al, Markus et al. Gutiérrez-Ortiz et al, Mao et al.	2020	389 + 18 + 59 + 11 + 1**= 478**	Anosmia	41.60%
Lee et al. Mao et al.	2020	354 + 12 + 144= **510**	Ageusia	44.40%
Francesco et al.	2020	**1**	CVT	0.09%
Ahmad et al. Mao et al.	2020	26 + 16= **42**	Delirium	3.70%
Vollono et al. Moriguchi et al.	2020	**2**	Meningitis/ Encephalitis	0.17%
Ahmad et al.	2020	**107**	Encephalopathy	9.30%
Beyrouti et al. Markus et al. Co et al. Ahmad et al. Avula et al.	2020	88 +6 +1 + 8 + 4= **107**	Ischemic stroke	9.30%
Ahmad et al.	2020	7+1+1= **9**	Neuropathy	0.80%
Sedaghat et al.	2020			
Ottaviani et al.				

DISCUSSION

Arterial strokes: COVID-19 itself is deemed a risk factor for ischemic stroke in studies from the United Kingdom and New York[9,10]. The incidence of stroke among PCR-positive COVID-19 patients is around 5%[11,12]. A correspondence published in April 2020 reported large-vessel ischemic strokes in five patients with COVID-19aged 50 years or below[13]. Patients with stroke may present clinically with confusion, dysphagia, dysarthria, numbness, and hemiparesis. Brain imaging and angiographic studies confirm thrombotic vascular occlusions and ischemic infarcts[10,12,13]. D-dimer, C-reactive protein, and fibrinogen levels are notably high[10] which relateto increased stroke severity, infarction volume, and subsequent 1-month disability[14].The laboratory parameters guide treatment plans, which comprises standard acute stroke treatment including acute IV thrombolysis and mechanical clot extraction[10,13]. Co CO et al. reported the case of acute ischemic stroke in female with COVID-19 that was managed with intravenous alteplase[14].Mechanisms of ischemic stroke are yet to be understood, and include cardioembolic secondary to pneumonia and sepsis, vasculitis with direct endothelial injury, and immune induced-hypercogaulopathic state including possibility of acquired antiphospholipid antibody syndrome (articles attached and look for more). Fewer cases of primary intracerebral hemorrhage have been reported[5,15]and risk factors include coexisting HTN and concurrent use of antithrombotic.Timely diagnosis and appropriate management can reduce stroke-related morbidity[12].

Cerebral Venous Thrombosis: Cerebral venous thrombosis (CVT)presents with a wide range of clinical spectra that is common in younger patients with a female to male ratio of 3:1[16]. CVT is a rare phenomenon that is seen with some frequency in young patients; while it is of multifactorial origin, gender-related causes are found[16,17].Notably, a prothrombotic state is a risk factor for CVTs in COVID-19 positive patients. With emerging neurological evidence about thrombotic complications and prothrombotic states, COVID-19 is a risk factor in precipitating episodes of CVTsCerebral vascular imaging ought to be considered in COVID-19 patients showing neurological signs and symptoms because CVT is recognized as a filling defect on cerebral CT angiography[16,17]. Prothrombotic state in a COVID-19 setting, even without a previously documented hypercoagulability, may account for CVT when other inherited and acquired causes (for example brain tumors, head trauma, and local central nervous system infection) have been excluded. Apart from in-hospital management with low-molecular-weight heparin, Hughes, et al, proposed prophylactic in-patient and post-discharge LMWH therapy for COVID-19 patients[16].

Encephalopathy/Delirium: Risk factors for delirium in COVID-19 patients include multi-organ failure, sedatives, prolonged mechanical ventilation, immobilization, and separation from family[18]. Encephalopathy and altered sensorium in COVID-19 infection were reported in 40% of patients[5]. One case of Acute necrotizing encephalopathy has been reported, diagnosed was suggested after brain MRIfindings of bilateral, hemorrhagic, multifocal thalamic lesions[19], however, there was no mention of histopathology report to exclude encephalitis.

Acute Encephalitis/ Meningo-Encephalitis/& Myelitis: The first case of encephalitis associated with COVID-19 was reported when RNA of SARS-CoV-2 was detected in the CSF specimen of the patient by PCR. This provided direct evidence of the neuro-invasiveness of COVID-19[20]. Additional pathological findings in brain tissue of COVID-19 positive cases are reported in the gross anatomy of the admitted patients due to the cerebral infarction diagnosed on the 13th day of admission [20]. COVID-19-associated meningoencephalitis has been reported in a 24-year-old male who presented with generalized seizures, cervicalstiffness and loss of consciousness after a 10-day history of flu-like symptoms. Bilateral ground-glass opacities on lung CT, hyperintense signals on MRI brain, raised CSF white cell count and PCR-detection of SARS-CoV-2 RNA in the CSF by PCR helped in diagnosis. However, the specific SARS-CoV-2 RNA was undetected in the nasopharyngeal swab, indicating that a negative pharyngeal swab PCR cannot rule out COVID-19 infection[21].Another 40-year-old man with COVID-19 reported having rhombencephalitis based on MRI findings presented with gait imbalance, diplopia, nystagmus, and limb ataxia[22].A third patient with flaccid lower limb weakness and persistent fever in COVID-19 infection has also been reported to have acute myelitis[22].Therefore, neurological inspection and attempts to distinguish SARS-CoV-2 from the neuronal tissue are necessary to establish neurotropic evidence of the virus[20].

Seizures/Epilepsy: Historically, the group of coronaviruses have been found to affect the central nervous system leading to neurological indications[24]. However, seizures have not been reported as a neurological manifestation of COVID-19 disease. In two COVID-19 patients who had elevated risk for developing seizures, the origin of seizures was found to be multifactorial. Electrography has been used to monitor COVID-19 patients for seizures[24]. A case report finds a 30-year-old healthy female patient with recurrent generalized tonic-clonic seizures[24]. In these reported cases, the brain MRI findings are normal, and the CSF is negative for RNA of SARS-CoV-2 upon discharge[5].COVID-19 patients primarily present with myoclonic jerks or focal status epilepticus, with characteristic abnormal electroencephalogram findings. Investigations excluded encephalitis and cerebral infections. Management with antiepileptics is likely to control seizures.Antiepileptics can controlseizures, which can occur in encephalitis[7,21]. Another case report presented a 72 years old positive tested patient with sudden onset of seizures. Patient had

no previous medical history of seizures. To conclude, patients with sudden onset of seizures having common symptoms of Coronavirus disease should be tested for SARS COV-2[25].

Anosmia & Ageusia: Upper respiratory tract infections may cause a mild reduction in smell and taste sensation[1,26]. COVID-19 is associated with a partial or total loss of smell (hyposmia and anosmia respectively) and taste disturbances. These findings were indicated in case series of five COVID-19 patients from Iran who developed acute anosmia and taste dysfunction[1]. New-onset anosmia and ageusia is common in patients with COVID-19[23]and maybe the only manifesting symptom[26,27]. It is reversible and highly common in younger patients[26,28]. Anosmia may only unveil on standardized screening procedures such as the Burghart-Sniffin' Stick test; however, it does not predict disease severity[29]. Lee Y, et al. reported sudden anosmia and ageusia in 15.3% patients with COVID-19 in the early stage and 15.7% of patients with asymptomatic to mild disease[26]. In a prospective cross-sectional study conducted in Germany, anosmia was found in 40% of 45 hospitalized patients with COVID-19, and in none of the 45 uninfected controls[29]. These studies suggest early COVID-19 testing for people who report acute anosmia during the pandemic.

Acute peripheral neuropathy including Guillain-Barre Syndrome (GBS), Miller-Fisher syndrome and polyneuritis cranialis: Mao et al evaluated the neurological findings in 214 COVID-19 patients. Of all these patients that were hospitalized, 36.4% had neurological symptoms[30]. However, there was no reported GBS due to COVID-19 infection. GBS has a progressive, symmetrical, and ascending symmetrical flaccid limb paralysis[30]. SARS-CoV-2-associated peripheral neuropathy including Guillain-Barre Syndrome (GBS) has been reported in multiple case reports[30,31]. PCR-positive COVID-19 patients after a brief period of respiratory illness can develop hallmark symptoms of GBS such as acute symmetrical progressive ascending limb weakness, cranial nerve involvement, and ultimately respiratory failure. The assessment shows reduced muscle strength, areflexia, and sensory deficits. Albumino-cytological dissociation (raised proteins and normal cell count) in CSF, decreased action potential amplitudes, reduced conduction velocities on neurophysiological studies, and decreased recruitment on electromyography are observed. Along with supportive treatment for COVID-19, intravenous immunoglobulins are given for GBS management[30,31,32]. GBS associated with SARS-CoV-2 can occur concomitantly with the infection, instead of the typical post-infectious course[32,33].

Patient data from Spain finds that Miller Fisher syndrome is a rare finding during the COVID-19 pandemic[34]. Neurological findings may occur due to the aberrant immune system response to the virus[34]. The first patient identified in a case report presents treatment options such as intravenous immunoglobulin. Recovery includes complete neurological improvement excluding residual ageusia and anosmia[34]. Recent studies also report Miller-Fisher syndrome and polyneuritis cranialis in COVID-19 patients. GD1b-IgG antibodies are useful in diagnosing Miller-Fisher syndrome. GD1b-IgG antibodies and the absence of SARS-Cov-2 RNA in CSF of the patient with Miller-Fisher syndrome implied immune-mediated damage rather than a direct viral injury[34].

Post-GBS locked-in syndrome was reported in 51-year-old male COVID-19 patient, in which condition of GBS worsened despite treatment with intravenous immunoglobulins and plasma exchange therapy. The patient exhibited complete quadriplegia and sensory loss, bilateral facial and hypoglossal nerve paralysis and eventually respiratory failure warranting artificial ventilation. Bilateral contrast enhancement of nerve roots at all spinal levels with symmetrically-involved anterior and posterior nerve roots were found on MRI of the spine[35].

CONCLUSION

While COVID-19 largely affects the respiratory and the cardiovascular system, associated involvement of the nervous system may occur. Acute encephalitis, stroke, and GBS are the most clinically significant and life-threatening complications if not managed promptly. On top of that, neurological manifestations could present early during the COVID-19 course of illness. Pathogenesis includes direct and indirect mechanisms, which suggests effective antiviral treatment will only reduce their rate of occurrence, and neurologists have to be familiar with these complications.

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