Neurology of COVID-19

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TABLE OF CONTENTS

INTRODUCTION

Several neurological symptoms of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection or coronavirus disease 2019 (COVID-19) have previously been described in the literature. Several registries[1-3] and systematic reviews[4] have identified the various neurological manifestations of SARS-CoV-2 infection. Misra et al.[4] identified forty-one neurologic manifestations (24 symptoms and 17 diagnoses) in a review of 350 studies providing data on 145,721 patients with SARS-CoV-2 infection. These neurological diseases include cerebrovascular diseases, encephalitis or encephalopathy, headache, epilepsy, status epilepticus, Guillain-Barre syndrome, Miller-Fisher syndrome, para-infectious radiculitis, critical illness polyneuropathy/myopathy, rhabdomyolysis, posterior reversible encephalopathy syndrome, anosmia, ageusia or dysgeusia, dysexecutive syndrome, dysautonomia, restless leg syndrome, dizziness, ataxia, and neurocognitive deficits. Some of these manifestations are seen in patients with any viral illness, and some are either unique or seen in higher rates in patients with SARS-CoV-2 infection. The presence of neurologic manifestations in patients with SARS-CoV-2 was associated with almost twofold higher mortality.[4] Several neurological manifestations are seen in the post-infectious period after SARS-CoV-2 infection and are considered part of post-COVID or long COVID syndrome. The Centers for Disease Control and Prevention (CDC) identified difficulty thinking or concentrating (sometimes referred to as "brain fog"), headaches, sleep problems, dizziness when you stand up (lightheadedness), pins-and-needles feelings, changes in smell or taste, and depression or anxiety.[5] As of July 2021, several of these conditions can be considered disabilities under the Americans with Disability Act.[6]

The pathophysiology of neurological manifestations is broadly divided into neurological injury and intravascular thrombosis secondary to immune activation[7,8] and those related to direct entry of the virus into the central nervous system.[9,10] Neural immunoglobulin G (IgG) antibodies against the SARS-CoV-2 spike glycoprotein are associated with immune-mediated encephalitis,[8] and the consequent endothelial damage, in addition to inflammation-related platelet activation, initiates thrombotic events in the cerebral circulation.[11] The SARS-CoV-2 spike protein interacts with

angiotensin-converting enzyme 2 (ACE2) expressed in the capillary endothelium and subsequently, damages and enters through the endothelium (blood-brain barrier) to interact with ACE2 receptors in neuronal tissue.[12] SARS-CoV-2 can use olfactory neurons (or other nerve tracts) to enter the central nervous system.[9,10,13] The underlying pathophysiology may be multifactorial, and multiple pathways may overlap in the same neurological diseases associated with SARS-CoV-2 infection.

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CHAPTER 1

ENCEPHALOPATHY ASSOCIATED WITH SARS-COV-2 INFECTION

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Introduction

Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a global pandemic by the World Health Organization (WHO) in March 2020. In most cases, COVID-19 presents with fever and respiratory tract symptoms; however, cardiac, gastrointestinal, renal, neurological, hematological, and cutaneous manifestations can occur. The neurological manifestations reported in afflicted individuals can affect the central and peripheral nervous systems and the skeletal musculature.

Encephalopathy is a broad term used to describe any global or focal brain disturbances that result in cognitive dysfunction. Encephalopathy can occur due to a toxic or metabolic cause, or chronic systemic conditions. Neurological causes include cerebrovascular disease, seizures, trauma, infections, acute demyelination, neoplasms, and neurodegenerative diseases. Delirium is a clinical presentation of encephalopathy that results in altered mentation with waxing and waning attention.[1,2] Studies indicate that 20-30% of COVID-19 patients can develop altered mentation during the course of their hospital stay, with rates increasing up to 70% in severe cases among all age groups.[3]

Definitions and terminology

The terms "delirium" and "acute encephalopathy" are frequently used interchangeably. There is an effort by medical organizations to develop a person-centered model, review the terminology, and consider ‘delirium spectrum disorder’ as a possible term to encompass the underlying brain

dysfunction (encephalopathy) leading to a variety of phenotypes (delirium) that range from underactive to hyperactive with varying ages, etiologies, and comorbidities.[4] Delirium describes a clinical state that meets the diagnostic criteria for delirium underlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), listed in **Table 1**. It involves attentional disruption leading to impairment in the ability to direct, sustain, and shift focus. This results in reduced orientation to oneself, their environment, and time.[5]

Table 1: Diagnostic criteria for delirium

Disturbance of attention (decreased ability to direct, focus, persist, and shift attention) and awareness (decreased orientation towards the environment) • Develops over hours to few days • Indicates a change from baseline • Fluctuating severity throughout the day
Disturbance of cognition including memory, orientation, language, visuospatial ability, or perception
Disturbance of attention, awareness, and cognition- • Unexplained by established and evolving neurocognitive disorders • Not occurring in the setting of markedly reduced level of consciousness
Evidence indicating the etiology that resulted in the disturbance- • Delirium due to another medical condition • Substance intoxication delirium • Substance withdrawal delirium • Delirium due to multiple etiologies- - Timeline: Acute (lasting few hours or days) or persistent (lasting weeks or months) - Level of activity: Hypoactive, hyperactive, or mixed level of activity

A panel of leading experts in intensive care, neurology, geriatrics, rehabilitation medicine, pharmacy, anesthesiology, and psychiatry developed a consensus recommendation on nomenclature. Acute encephalopathy was defined as a rapidly developing (hours to <4 weeks) pathobiological process in the brain that can lead to the clinical presentation of sub-syndromic delirium, delirium, reduced level of consciousness or coma; all representing a change from baseline cognitive status.[6]

Epidemiology

The exact incidence of COVID-19-associated encephalopathy is still not available due to a lack of prospective systematic screening in patients with SARS-CoV-2 infection. However, there are multiple studies evaluating encephalopathy in affected patients, including large observational studies, case series, and case reports.

Shao et al.[7] conducted a comprehensive literature review of 48 studies with 11,553 COVID-19 patients from 13 countries. Pooled prevalence, incidence, and mortality rates for delirium in COVID-19 patients were 24.3%, 32.4%, and 44.5%, respectively (see Figures 1-3). For patients aged over 65 years, prevalence, incidence and mortality rates for delirium in COVID-19 patients were 28.2%, 25.2%, and 48.4%, respectively. For patients under 65 years, prevalence, incidence, and mortality rates for delirium in COVID-19 patients were 15.7%, 71.4%, and 21.2%, respectively. Overall, COVID-19 patients with delirium suffered a higher risk of mortality compared with those without delirium (odds ratio [OR]: 3.2, 95% confidence interval [CI] 2.1-4.8). Misra et al.[8] reviewed 350 studies providing data on 145,721 patients with COVID-19, 89% of whom were hospitalized. The prevalence of encephalopathy-related diagnoses was as follows: acute confusion/delirium 11% (95% confidence interval (CI) 7%–16%, 19 studies); disturbance of consciousness 7% (95% CI: 5%–10%, 25 studies); and agitation 45% (95% CI: 3%–93%, 3 studies). In patients with COVID-19 ≥60 years of age, the pooled prevalence of acute confusion/delirium was 34% (95% CI: 23%–46%, 5 studies).

A summary of relevant studies is provided in **Table 2**[10-21] below.

Table 2. Summary of studies evaluating prevalence and risk factors for encephalopathy associated with COVID-19

Study	Outcome (definition)	Patient population	Prevalence	Risk factors
Abenza Abildúa et al.[9]	Encephalopathy is defined as brain dysfunction in one or more of its functions (alterations of consciousness, seizures, confusion, and/or focal neurological deficits produced by a systemic disease: anoxic, ischemic, metabolic, etc., usually reversible.	Total of 232 patients with neurological manifestations	51 (21.9%)	Hypertension, previous epilepsy, cognitive impairment, or stroke
Dimitriadis et al.[10]	Encephalopathy (=delirium, disorder of consciousness, hypoxic encephalopathy, encephalopathy not further described).	A total of 392 patients in intensive care unit	181 (46.17%)	Older age, history of ischemic stroke, hypertension, diabetes mellitus, nicotine consumption, dyslipidemia
Frontera et al.[11]	Toxic encephalopathy was coded for patients with temporary/ reversible changes in mental status in the absence of focal neurologic deficits or primary structural brain disease, excluding patients affected by sedatives or other drugs or hypotension (mean arterial pressure).	A total of 4491 hospitalized patients	559(78%)	Older age, men, past neurological history (dementia, ischemic stroke, seizure, or movement disorder), psychiatric history, chronic kidney or liver disease, hypertension, diabetes mellitus, and coronary artery disease

Helms et al.[12]	Delirium was defined by a positive Confusion Assessment Method for the intensive care unit at least once during the intensive care unit stay and was classified into hypo- or hyperactive delirium according to the clinical presentations	Total of 140 patients in intensive care unit	118 (84.3%)	Stroke/transient ischemic stroke, partial epilepsy, mild cognitive alteration, migraine, traumatic brain injury, aneurysm, diabetes mellitus, chronic kidney diseases, chronic liver disease, respiratory diseases (chronic obstructive pulmonary disease, asthma, obstructive sleep apnea), malignancies/ hemopathies, cardiovascular diseases
Kennedy et al.[13]	Delirium identified through a reliable and widely used medical record review, as validated against the Confusion Assessment Method	Total of 817 patients in emergency department	226 (28%)	Age>75 years, living in nursing homes, prior psychoactive medications, vision impairment, stroke Parkinson disease
Kotfis et al.[14]	Delirium was identified through retrospective chart review according to DSM-5 criteria if present at least once during hospitalization	Total of 201 hospitalized patients	39 (19.4%)	Diabetes mellitus, hypertension, chronic kidney disease, chronic heart failure

Liotta et al.[15]	Encephalopathy identified by (a) report of altered mental status or depressed level of consciousness, (b) physician documented diagnosis of encephalopathy or the delirium encephalopathy syndrome, or (c) positive Confusion Assessment Method evaluation	A total of 509 hospitalized patients	162 (31.8%)	Hypertension, cigarette smoking, chronic kidney disease, dyslipidemia, heart failure, cancer
Maamar et al.[16]	Agitation was defined as a day with the Richmond Agitation Sedation Scale greater than 0 after exclusion of other causes of delirium and pain.	A total of 241 patients in intensive care unit	111 (46.1%)	Hypertension, obesity, diabetes mellitus, previous neurologic history
Marra et al.[17]	"Encephalopathy" used as a clinical bridge for the multiple and varying degrees of descriptors used to diagnose acute Central Nervous System impairments. Such descriptors included altered mental status, disorientation, impaired consciousness, and encephalopathy itself.	Total of 36615 hospitalized patients	1133 (3.1%)	Asthma, hypoxemia, diabetes mellitus, hypertension, chronic kidney disease, obesity, tobacco use, immunodeficiency, chronic obstructive pulmonary disease
Pun et al.[18]	Delirium was identified from the medical records according to a validated record review approach.	Total of 2088 patients in intensive care unit	1704 (81.6%)	Congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, liver disease, renal disease

Ragheb et al.[19]	Delirium was defined by the presence of either of the following criteria: (1) a positive Confusion Assessment Method screen 22 as conducted by the bedside nurse, or (2) the presence of an acute confusional state, as documented in the medical record and elucidated via a validated, standardized chart review method.	A total of 148 patients in intensive care unit	108 (73%)	Hypertension, diabetes mellitus, obesity
Scullen et al.[20]	Patients were categorized as having "COVID-19-associated encephalopathy" if they had either scalp electroencephalography showing either generalized encephalopathy or epileptic encephalopathy as well as changes on computed tomography and/or magnetic resonance imaging of the head.	A total of 76 patients in intensive care unit	20 (74%)	Hypertension, type 2 diabetes mellitus, obesity, chronic kidney disease
Wong et al.[21]	Assessed delirium using a validated chart review tool that is based on the occurrence of key words (e.g., agitation, confusion) when a diagnosis of delirium is not documented.	A total of 927 hospitalized patients	497 (53.6%)	Hypertension, diabetes mellitus and coronary artery disease

Apart from the larger studies, multiple case series and single cases have reported encephalopathy as a severe complication of SARS-CoV-2 infection.[22,23] Cervantes-Arslanian et al.[24] analyzed the data from the Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study COVID-19 Registry and reported that 1656 (10%) out of 16,225 patients with SARS-CoV-2 infection developed encephalopathy. A prospective cohort study published in June 2020 identified 257 critically ill adults with COVID-19 in New York City and analyzed the epidemiology, clinical course, and outcomes of these patients. At least one form of chronic illness like hypertension, diabetes mellitus, or obesity was present among 212 of these patients, and altered mental status was reported in 23 (9%) individuals. An observational study published in June 2020 studied the neurologic features in 58 patients with severe SARS-CoV-2 infection. Delirium was observed in 40 (69%) patients, and corticospinal tract signs were demonstrated in 39 (67%) patients.[25] Another single-center retrospective analysis[20] published in September 2020 described central nervous system manifestations in critically ill COVID-19 patients. A total of 27 patients were analyzed, of which 20 (74%) patients had encephalopathy, 2 (7%) had acute necrotizing encephalopathy, and 5 (19%) had vasculopathy.[20] Another retrospective cohort study in March 2020[26] reported that hypoxic-ischemic encephalopathy (23;20%) was the most common neurological manifestation among 113 COVID-19 patients who died. Acute respiratory syndrome (ARDS), sepsis, acute myocardial injury, heart failure, electrolyte abnormalities, and acute renal failure were considered the contributing factors for hypoxic encephalopathy.

Encephalopathy may be the primary symptom of SARS-CoV-2 infection. In a study of 817 older patients (median age 78 years) evaluated in the emergency department who were diagnosed with COVID-19, encephalopathy was present in 28% of the patients.[13] Among those patients, 37% lacked typical SARS-CoV-2 infection symptoms such as fever or dyspnea. Patients with SARS-CoV-2 infection may be at higher risk for encephalopathy compared with other viral infections. Maamar et al.[27] reported that patients with SARS-CoV-2 infection had significantly higher rates of agitation than patients with influenza (54.8% versus 32.6%, $p < 0.01$).[27] After matching with a propensity score, patients with SARS-CoV-2 infection continued to have significantly higher rates of agitation than influenza patients (51.6% vs.. 33.7%, $p = 0.006$).

Effect on outcome

Encephalopathy in patients with SARS-CoV-2 infection has been associated with both short- and intermediate-term adverse consequences. A retrospective study of COVID-19 patients demonstrated an increased in-patient morbidity and mortality in those who developed neurological manifestations.[28] Liotta et al.[15] reported that among hospitalized patients with COVID-19, encephalopathy was independently associated with worse functional outcomes and higher mortality within 30 days of hospitalization (21.7% vs.. 3.2% of patients). Cervantes-Arslanian et al.[24] analyzed the data from the Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study COVID-19 Registry and reported that patients with encephalopathy were more likely to be admitted to the intensive care unit (ICU) and had higher mortality during hospitalization, ICU stay, and at 28 days post infection. Harivanto et al.[29] performed a systematic review of 20 studies and found that delirium symptoms on admission were associated with poor outcomes from SARS-CoV-2 infection [odds ratio [OR] 2.36] and its subgroup which consists of severe SARS-CoV-2 infection [OR 3.89], and mortality from COVID-19 [OR 1.90]. Meta-regression showed that the association was influenced by the age of the patient ($p = 0.005$). Pranata et al.[30] performed a systematic review, including 3,868 patients from 9 studies. The proportion of patients with delirium was 27% [95% CI: 20%-34%]. Delirium was associated with mortality (OR 2.39). A pooled adjusted analysis indicated that delirium was independently associated with mortality (adjusted OR 1.50). A subgroup analysis of delirium assessed at admission indicates an independent association (OR 1.40). Meta-regression indicated that the association between delirium and mortality was not significantly influenced by study-level variations in age, gender, hypertension, diabetes mellitus, and dementia. Ragheb et al.[19] reported that 24% of patients with SARS-CoV-2 infection who had delirium during hospitalization, later screened positive for delirium at home based on caretaker assessment, 23% demonstrated signs of questionable cognitive impairment or cognitive impairment consistent with dementia, and 12% screened positive for depression within 2 months after discharge.[19] In another series, patients without any abnormalities on magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) were most likely to recover earlier.[28]

Risk factors

The risk factors are summarized in **Table 3.** Pun et al.[18] reported that older age, Simplified Acute Physiology Score (SAPS) II scores, cigarette smoking or alcohol abuse, invasive mechanical ventilation, vasopressors, restraint use, antipsychotics, sedative benzodiazepine infusions, and continuous opioid infusions were each associated with a higher risk of delirium the next day. Family visitation was associated with a 27% lower risk of delirium. A history of stroke or neurologic disorder increased the odds of developing a neurologic manifestation, and specifically dementia, conferred the highest risk of all factors identified.[31] Pranata et al.[30] reported that every 1 mg/L increase in C-reactive protein was significantly associated with a 1% increased risk of delirium.[30] Cervantes-Arslanian et al.[24] and Kennedy et al.[13] identified age older than 75 years, living in a nursing home or assisted living, prior use of psychoactive medication, vision impairment, hearing impairment, stroke, and Parkinson's disease as risk factors for delirium associated with COVID-19.

Table 3. Summary of all the risk factors for encephalopathy associated with COVID-19 adapted from Cervantes-Arslanian et al.[24] and Pun et al.[18]

RISK Factor	**OR**	**95% C.I.**	**P-value**
Race			0.002
American Indian or Alaska Native	0.66	(0.40- 1.11)	0.119
Black or African American	1.33	(1.09- 1.61)	0.005
Mixed race	0.43	(0.26- 0.71)	0.001
Other	0.83	(0.66- 1.04)	0.097
South Asian	0.38	(0.19- 0.77)	0.007
Unknown	1.02	(0.73- 1.41)	0.924
West Asian	0.66	(0.43- 1.00)	0.052
Age	1.24	(1.21- 1.28)	<0.001
Hypertension	1.03	(0.89- 1.19)	0.693
Cardiac arrythmia	0.85	(0.73-0.97)	0.020
Diabetes mellitus	0.87	(0.78- 0.97)	0.017
Coronary artery disease	0.96	(0.84- 1.10)	0.539
Disease severity			<0.001
3	0.74	(0.63- 0.87)	<0.001
4	0.60	(0.51- 0.70)	<0.001
5	0.57	(0.47-0.68)	<0.001
6	0.92	(0.76- 1.11)	0.377
7	1.04	(0.84- 1.29)	0.733

Age at hospital admission (71 vs. 55 years)	1.13	1.03-1.25	0.036
SAPS II score at baseline (54 vs. 32)	1.17	(1.07-1.29)	0.0013
Sex (women vs. men)	0.97	(0.85-1.11)	0.67
Vision or hearing impairment (yes vs. no)	0.94	(0,71-1.25)	0.68
Current smoker or alcohol abuse (yes vs. no)	1.37	(1.13-1.67)	0.0013
Ventilation type (invasive mechanical ventilation vs. none or nasal canula)	1.48	(1.17-1.87)	0.0013
Ventilation type (non-invasive mechanical ventilation vs. none or nasal canulal)	1.13	(0.86-1.49)	0.0013
Ventilation type (high- flow nasal cannula vs. none or nasal cannula)	1.04	(0.81-1.34)	0.0013
Vasopressors (yes vs. no)	1.25	(1.10-1.43)	0.0009
Position (prone vs. supine)	0.88	(0.71-1.09)	0.24
Restraint use (yes vs. no)	1.32	(1.16-1.50)	0.0001
Sedative infusion (benzodiazepine vs. non0benzodiazepine)	1.59	(1.33-1.91)	0.0001
Sedative infusions (none vs. non benzodiazepine)	0.94	(0.81-1.09)	0.0001
Continuous opioid infusion (yes vs. no)	1.39	(1.21-1.60)	0.0001
Antipsychotics (yes vs. no)	1.59	(1.36-1.85)	0.0001
Oral anxiolytics (yes vs. no)	1.01	(0.88-1.15)	0.92
Proportion of ABCDE elements performed (0.75 vs. 0.50)	0.94	(0.88-1.01)	0.17
Visitation from family or friends (yes vs. no)	0.73	(0.63-0.84)	<0.0001

Disease severity is based on an ordinal scale proposed by the World Health Organization (WHO) to measure the disease severity due to COVID-19.[32]

Clinical Presentation

Patients who develop encephalopathy present in a similar fashion to other forms of encephalopathy with delirium, agitation, or coma.[33] Generally, delirium develops over hours to days (rarely over a week) as a change from

baseline, presenting with fluctuating levels of alertness, orientation, and behavior. A prodromal phase may precede the onset of overt delirium by hours to even weeks. Subtle features that can easily be missed include poor concentration, sleep issues like vivid dreams, tiredness, irritability, restlessness, or even noise sensitivity with some features predicting delirium regardless of predisposing factors.[2] While most reported cases of delirium in COVID-19 patients occur in severe cases, elderly individuals, and those with underlying comorbidities,[34] one study has also reported that encephalopathy with altered mental status ranging from mild to obtunded occurred in a young cohort of COVID-19 patients with a high proportion of comorbidities. They hypothesize that regardless of age, the presence of comorbidities is responsible for the severe course of the encephalopathy.[20] There have also been reports of COVID-19-associated encephalopathy and delirium developing before any respiratory changes in otherwise previously healthy individuals.[35] Though considered very rare, multiple forms of encephalopathy have been reported during the course of COVID-19. Some of the forms include acute epileptic encephalopathy,[36] hemorrhagic posterior reversible encephalopathy syndrome (PRES),[37] and acute necrotizing encephalopathy.[38] The occurrence of encephalopathy associated with SARS-CoV-2 infection can be differentiated from other forms of encephalopathy by the presence of partial or complete anosmia and ageusia.[33]

Girard et al.[31] reported 51 cases of encephalopathy or encephalitis in the Spanish Society of Neurology's COVID-19 Registry. The most frequent syndromes were mild or moderate confusion (33%), and severe encephalopathy or coma (9.8%). The mean time between the onset of infection and the onset of neurological symptoms was 8 days. For Helms et al.,[25] the study had the neurologic findings recorded in 8 of the 58 patients (14%) on admission to the ICU (before treatment) and in 39 patients (67%) when sedation and a neuromuscular blocker were withheld. Agitation was present in 40 patients (69%) when neuromuscular blockade was discontinued. A total of 26 out of 40 patients were noted to have confusion according to the Confusion Assessment Method for the ICU. These patients had a score of −1 to 1 on the Richmond Agitation and Sedation Scale, on a scale of −5 [unresponsive] to +4 [combative]. Diffuse corticospinal tract signs with enhanced tendon reflexes, ankle clonus, and bilateral extensor plantar reflexes were present in 39 patients (67%). Of the patients who had been discharged, 15 of 45 (33%) had a dysexecutive syndrome consisting of inattention, disorientation, or poorly organized movements in response to commands. Pun et al.[18] found the median duration of coma was 10 days, and 3 days for delirium in patients with COVID-19-related encephalopathy. The median duration of hyperactive delirium was 2 days in almost half of the

patients. The duration of encephalopathy was longer than seen in other ICU admissions, where the median duration of coma was 1 day and that of delirium was 4 days, for a total of 5 days.[18]

Approaching Encephalopathy/Delirium

Delirium can occur in COVID-19; however, the occurrence of neurological symptoms in the absence of other manifestations, the pathophysiology, and the treatment of affected individuals still remain to be understood. Some authors consider delirium a vital sign of severe illness in older adults and recommend that it be included as part of the screening criteria due to the increased risk of overlooking potential SARS-CoV-2 infections.[3]

Screening tools

In general, a major number of delirium cases go unrecognized, indicating the importance of effective screening for prompt diagnosis and treatment. Several screening tools are available to diagnose delirium, and one of the screening methods used to diagnose delirium is the Confusion Assessment Method (CAM) diagnostic algorithm. It can be performed in 5 minutes and uses four criteria: acute change of mental status with a fluctuating course, deficits with attention, disorganized thinking, and altered levels of consciousness. The presence of the first and second criteria and either the third or fourth criterion is required for the diagnosis of delirium.[39] Studies have shown CAM to be 82% sensitive and 99% specific for the accurate detection of delirium.[40]

For patients in the ICU, a brief intensive care screening checklist with 99% sensitivity and 64% specificity has proven to be useful in comparison to other screening tests. It includes evaluating patients for altered levels of consciousness, inattention, disorientation, hallucination or delusion, psychomotor agitation or retardation, inappropriate mood or speech, sleep/wake cycle disturbance, and symptoms fluctuation.[41] The Confusion Assessment Method for the ICU (CAM-ICU) test can also be applied to these patients, which uses nonverbal responses to assess attention, thinking, and level of consciousness.[42]

History and Physical Examination

Acquiring a thorough history, primarily from the caregivers of the patient, and a mental status evaluation are essential for the diagnosis of delirium.

However, the ongoing pandemic has brought upon several challenges that create a viable atmosphere for delirium, as mentioned below:[43]

- There is limited contact between the patient's family or caregivers and the healthcare personnel. This makes it difficult to acquire a proper history while hindering delirium prevention strategies like providing reassurance, reorientation, and other forms of family support.
- The use of protective gear by healthcare personnel can frighten a confused individual and hinder effective communication.
- Continuous attachment of monitoring devices to patients can also increase the risk of delirium.

The failure to detect delirium from SARS-CoV-2 infection can lead to[44,45]

- Missing the diagnosis of COVID-19 and further accelerating the spread of the infection.
- Increased mortality from lack of acknowledgment of the severity of infection.
- Increased risk of long-term cognitive and functional effects.

Pathogenesis

The novel SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus. The specific neuropathological mechanism by which the virus invades the CNS is still unknown.[46] Studies have shown that a relatively large proportion of COVID-19 patients present with neurological symptoms during the disease course, and that the prevalence is higher in severe or critically ill individuals.[47] Various studies that detect the presence of viral genetic material in brain tissue may indicate the neuroinvasive nature of SARS-CoV-2. Studies have detected the presence of SARS-CoV-2 in the CSF using real-time reverse transcription polymerase chain reaction (RT-PCR).[48] One study detected the presence of viral particles in the cytoplasm of the frontal lobe neurons and endothelial cells of the brain.[49] An autopsy series done on 27 patients detected the presence of viral proteins in multiple organs, including the brain.[50] Even though viral proteins have been detected in neural tissue, there is strong data suggesting that the virus was not detectable in the majority of patients with proven SARS-CoV-2 infections who developed neurological symptoms.[51,52]

Direct invasion

The direct viral entry into the central nervous system can be the simplest explanation for the neurological manifestations of SARS-CoV-2 infection. Epidemiological data suggest an incubation period of 5-14 days, which provides a considerable amount of time for viral entry into the central nervous system.[53] Viral proteins and genetic material can invade the nervous system through endothelial infection, leukocyte activation and migration, as well as olfactory neural transmission. The entry of SARS-CoV-2 viral proteins into the bloodstream following a pulmonary infection can further infect the epithelial or endothelial cells to cross the blood-brain or blood-CSF barrier, respectively, resulting in direct nerve cell damage. The involvement of the vascular endothelium can also result in the direct invasion of the neuronal glial cells. Leukocyte activation can also occur during an active infection, which can further cross the blood-brain barrier and cause neuronal damage through the production and release of proinflammatory cytokines and chemokines. Within the nervous system, astrocytic activation, which occurs in response to the infection, can add to the nerve damage by further increasing the chemokine production.[54,55] The immune mechanisms involved in SARS-CoV-2 infection are explained later in this chapter. Intranasal infection can result in the invasion of the nasal epithelium by the viral proteins, which then travel through the olfactory nerves and olfactory bulb to enter the forebrain and CSF to cause inflammation and demyelination.[56] This pathway could explain the symptoms of anosmia and ageusia, which is a common manifestation in COVID-19 patients.[57]

Cellular mechanisms

Angiotensin-converting enzyme-2 (ACE-2) is an aminopeptidase expressed in multiple human organ systems, including the brain and skeletal muscles.[58] Studies of other coronaviruses like SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) consider the ACE-2 interaction of viral proteins essential for cell entry.[59] The envelope glycoproteins of SARS-CoV-2, called spike proteins bind to ACE-2 receptors to gain access to host cells.[60] The results of a comparative study showed that SARS-CoV-2 spike proteins had a higher affinity for ACE-2 receptors in comparison to SARS-CoV glycoproteins, indicating that SARS-CoV-2 has a higher human-to-human transmissibility.[61] There are reports of the extensive-expression of ACE-2 receptors in the brain, further

indicating the potential for developing severe neurological manifestations via this mechanism.[62]

Cytokine storm

SARS-CoV-2 infection can cause a severe immune response by increasing leukocyte activation and elevations in proinflammatory cytokines and chemokines levels (**Table 4**).[63]

Table 4: Proinflammatory cytokines and chemokines involved with SARS-CoV-2 infection

Proinflammatory cytokines	Interferons (IFN): IFNα, IFNγ Interleukins (IL): IL-1β, IL-6, IL-12, IL-18, IL-33 Tumor necrosis factor (TNF): TNFα Tumor growth factor (TGF): TGFβ
Chemokines	CXC chemokine ligand (CXCL)10 CXCL8 CXCL9 CC-chemokine ligand (CCL)2 CCL3 CCL5

COVID-19 patients can develop cytokine storm syndrome due to the generalized, uncontrolled inflammatory response. The hallmark feature is lymphocytopenia, which occurs due to the lack of antibody production and suppression of adaptive immune system response.[64] The syndrome occurs over the first two weeks of infection and is characterized by a rapid and massive release of proinflammatory cytokines, leading to high fever, ARDS, and multiorgan failure.[65] Encephalopathy may occur due to high levels of cytokines in the CSF and result in the rare acute necrotizing hemorrhagic encephalopathy.[66] The pulmonary injury caused by a cytokine storm can result in ARDS and subsequent hypoxia or hypoxemia, causing multiorgan failure. The hypoxic-injury induced by respiratory failure can result in neurological manifestations like encephalopathy due to the close association of the lungs with respiratory centers in the brain stem.[67]

Impairment of the neurovascular unit

Bernard-Valnet et al.[68] reported a specific impairment of the neurovascular unit linked to intrathecal production of CXC chemokine ligand (CXCL)8 in a study of 22 patients who had presented with various neurologic presentations, including encephalopathy (n=12), encephalitis (n=2), myelitis (n=1), optic neuritis (n=1), Guillain-Barré syndrome (n=1), mononeuritis multiplex (n=1), and headache/vertigo (n=4).[68] SARS-CoV-2 RNA was measured by quantitative RT-PCR, SARS-CoV-2–specific antibodies, and 49 cytokines/chemokines/growth factors (by Luminex) in the CSF +/− sera of a cohort of 22 COVID-19 patients with neurologic presentation and 55 patients with either inflammatory neurologic disorder [IND], noninflammatory neurologic disorder, multiple sclerosis (MS), or neurological manifestations. Anti–SARS-CoV-2 immunoglobulin G was detected in patients with severe COVID-19 with some evidence of intrathecal synthesis. Of the 4 categories of tested patients, the CSF of inflammatory neurologic disorder exhibited the highest level of cytokines, chemokines, and growth factors. By contrast, patients with COVID-19 did not have evidence of upregulation of inflammatory mediators in the CSF. However, patients with severe COVID-19 (ICU patients) exhibited higher concentrations of CC-chemokine ligand (CCL)2, CXCL8, and vascular endothelium growth factor A (VEGF-A) in the CSF than patients with a milder form of COVID-19. In addition, intrathecal CXCL8 synthesis was linked to an elevated albumin ratio and correlated with the increase of peripheral inflammation (serum hepatocyte growth factor [HGF] and CXCL10), which supported impairment of the neurovascular unit.

Coagulopathy

SARS-CoV-2 infection is associated with both venous and arterial thromboembolic complications, resulting in venous thromboembolism, acute coronary syndrome, myocardial infarction, and ischemic strokes.[69] The extensive activation of the immune system can also stimulate the coagulation pathway, producing a hypercoagulable state. Cytokine release and cerebral thromboembolic events have been implicated in the pathogenesis of COVID-19 encephalopathy.[70] Patients with COVID-19 had prolonged prothrombin time and activated partial thromboplastin time, increased D-dimer and fibrinogen degradation products levels, as well as sepsis-induced coagulopathy which is a form of disseminated intravascular coagulation.[71,72] Furthermore, hypoxia due to respiratory failure can increase the viscosity of blood, increasing the risk of thrombosis.[73] Studies

have suggested that the presence of extensive coagulopathy is a major cause of mortality among young COVID-19 patients with no other comorbidities.[74]

Investigations

The diagnosis of encephalopathy secondary to COVID-19 requires adopting a methodological approach. Due to the lack of identifying markers, it is challenging for the practicing physician to identify if encephalopathy is a non-specific manifestation of severe illness or a direct symptom of the virus itself. Some authors suggest a full workup for encephalopathy, including hypoxia, toxins, drugs, and metabolic derangements.[75] However, the use of neuroimaging, neurophysiology, or electroencephalography (EEG) in COVID-19 encephalopathy can be difficult due to:[76]

- The challenge of performing the tests in the ICUs on severely ill patients.
- The potential risk of exposing the medical care staff and diagnostic technicians to the infection.

Neuroimaging

Brain imaging is frequently used in patients who develop altered mental status during the course of the SARS-CoV-2 infection. The findings are diverse and depend on the patient population studied. Neuropathology of severe cases with encephalopathy suggests widespread cerebrovascular changes, including microhemorrhage, diffuse intravascular microthrombosis, and endotheliitis.[77-79] Similarly, brain MRI images of patients with encephalopathy frequently demonstrate ischemic strokes even when not clinically identified,[25,80,81] and may show microhemorrhages with associated leukoencephalopathy,[82] and white matter changes consistent with posterior reversible encephalopathy syndrome.[83]

Initial reports [84] demonstrated multifocal abnormal signals, possibly indicating a diffuse thrombotic microangiopathy with arterial and venous components. MRI demonstrated multifocal cortical infarcts associated with marked microvascular arterial thrombosis, where hyperdense veins were indicative of stagnant venous blood.[84] A retrospective study[8] described eight distinctive neuroradiologic findings on MRI in 37 critically ill COVID-19 patients. Patients demonstrated single or multiple patterns as described below:[85]

- Signal abnormalities in the medial temporal lobe.
- Ovoid hyperintense lesions on fluid-attenuated inversion recovery (FLAIR) and diffusion sequences in the central part of the splenium of the corpus callosum.
- Non-confluent white matter hyperintense lesions on FLAIR and diffusion sequences with variable enhancements.
- Non-confluent white matter hyperintense lesions on FLAIR and diffusion sequences with variable enhancements and associated hemorrhagic lesions.
- Acute necrotizing encephalopathy- characterized by symmetric lesions of the thalamus and variable white matter lesions involving the brainstem, putamen, internal capsule, cerebrum, and cerebellum.
- Extensive and isolated white matter microhemorrhages.
- FLAIR sequence demonstrating extensive and confluent supratentorial white matter hyperintensities.
- Hyperintense lesions of bilateral middle cerebellar peduncles on FLAIR sequence.

In a prospective study[86] on 19 patients who had died of COVID-19, an early postmortem structural brain MRI identified parenchymal brain abnormalities in the form of subcortical micro and macro bleeds, cortico-subcortical edematous changes (similar to PRES), and nonspecific changes of the deep white matter. Furthermore, asymmetric olfactory bulbs were noted in a few subjects with no abnormalities of the olfactory tract. An observational study[87] performed MRI on 14 patients for unexplained encephalopathy with SARS-CoV-2. The authors noted enhancement of leptomeningeal spaces and bilateral frontotemporal hypoperfusion on perfusion imaging in a few patients. Few patients also demonstrated acute and subacute ischemic stroke with signal abnormalities noted with diffusion-weighted imaging. Another retrospective study[88] reported MRI findings of 11 critically ill COVID-19 patients who underwent brain imaging for altered levels of consciousness and reported: 1/. Diffuse leukoencephalopathy- confluent and symmetric T2 hyperintensity with mild restricted diffusion affecting bilateral supratentorial deep and subcortical white matter; and 2/. Juxtacortical and callosal microhemorrhages – multiple punctate microhemorrhages (<3mm) in the white matter of the juxtacortical region and corpus callosum, especially the splenium.

Another review article[5] described the distinct spectrum of neuroimaging features reported in COVID-19 patients:[33]

- Signal changes on T2/FLAIR imaging in the white matter of cortical and/or subcortical regions.
- Signal changes in the white matter associated with microhemorrhages.
- Bilateral, symmetric, and hemorrhagic lesions of the thalamus.
- Posterior reversible leukoencephalopathy (PRES).
- Signal changes on T2/FLAIR imaging in the medial temporal lobes and hippocampus- seen with autoimmune encephalitis.
- Multifocal white matter hyperintensities on T2/FLAIR imaging-seen with acute disseminated encephalomyelitis.
- Periventricular hyperintensities on T2/FLAIR imaging.
- Leptomeningeal enhancement.

Helms et al.[87] performed MRI of the brain on 13 patients. Although these patients did not have focal neurological deficits, they underwent MRI because of unexplained encephalopathy. Enhancement in leptomeningeal spaces was noted in 8 patients, and bilateral frontotemporal hypoperfusion was noted in all 11 patients who underwent perfusion imaging.[87] Two asymptomatic patients each had a small acute ischemic stroke with focal hyperintensity on diffusion-weighted imaging and an overlapping decreased apparent diffusion coefficient, and one patient had a subacute ischemic stroke with superimposed increased diffusion-weighted imaging and apparent diffusion coefficient signals. Kremer et al.[85] reported the results of MRI studies in 37 patients with severe COVID-19, most of whom had symptoms consistent with encephalopathy. The most common neurologic manifestations were alteration of consciousness (27 of 37, 73%), abnormal wakefulness when sedation was stopped (15 of 37, 41%), confusion (12 of 37, 32%), and agitation (seven of 37, 19%). The most frequent MRI findings were signal abnormalities located in the medial temporal lobe in 16 of 37 patients (43%), nonconfluent multifocal white matter hyperintense lesions seen with fluid-attenuated inversion recovery, and diffusion-weighted sequences with variable enhancement, with associated hemorrhagic lesions in 11 of 37 patients (30%), and extensive and isolated white matter microhemorrhages in 9 of 37 patients (24%). A majority of patients (20 of 37, 54%) had intracerebral hemorrhagic lesions with a more severe clinical presentation, a higher admission rate in ICUs (20 of 20 patients [100%] vs. 12 of 17 patients without hemorrhage [71%], $P = .01$), and the development of acute respiratory distress syndrome (20 of 20 patients [100%] vs. 11 of 17 patients [65%], $P = .005$). Kremer et al.[4] further reported on 64 patients;[81] thirty-six (56%) brain MRIs were considered abnormal, possibly related to SARS-CoV-2. Ischemic strokes (27%), leptomeningeal enhancement (17%), and encephalitis (13%) were the most frequent neuroimaging findings. Confusion