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Case Report

Rare case study of Covid agitation: The novel sinner causes a diagnostic dilemma

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ABSTRACT

COVID-19 pandemic has taught us a whole new set of medical terminologies. Since its inception, COVID-19 has claimed millions of lives and continues to haunt mankind. CNS manifestations of COVID-19 haven't been explored thoroughly and leave a grey area in current knowledge. Since most of the cases with CNS manifestations have been ignored and reached higher centers very late, the mortality rate has been high and further study has been limited in this subset.

Here 02 cases of COVID-associated CNS infection presenting with atypical neurological symptoms have been reported who could have been easily misdiagnosed and treated inadequately causing abysmal results. MRI brain combined with SARS-CoV-2 RNA testing are the mainstay diagnostic modalities clubbed with strong clinical suspicion.

COVID-19 was considered as a respiratory disease but the latest literature clearly highlights its multisystem involvement. CNS involvement in COVID-19 has been well-established now and needs to be treated aggressively and appropriately.

1. Introduction

In December 2019, Wuhan, witnessed an outbreak of pneumonia by an unknown etiological agent. On 7^{th} of January 2020, a group of Chinese scientists identified this virus as a previously unknown type of Coronavirus and named it 2019-nCoV (for 2019 novel coronavirus)[1,2] and soon, this COVID-19 virus had spread to many other countries having frequent visitors from China.[3] World Health Organization (WHO) officially announced this novel coronavirus disease on 11^{th} February 2020 as Coronavirus Disease 19 (COVID-19).[3] International Committee on Taxonomy of Viruses suggested the name SARS-CoV-2 for the virus that causes COVID-19.[4] 01 Month later on 11^{th} March 2020, World Health Organization declared this outbreak a pandemic.[5] The situation has worsened in leaps and bounds since then and 2021 has been hit worst by this.

The primary symptoms of COVID-19 include fever, dry cough, and fatigue.[6] However, some patients diagnosed with COVID-19 have not shown these typical symptoms at the time of diagnosis, instead, they exhibited only neurological symptoms at the prodrome. These symptoms were non-specific manifestations like headache, anosmia, diarrhea, malaise, and specific complaints like unstable walking, disorientation due to cerebral hemorrhage, cerebral infarction; as well as other neurological diseases.[7] Even

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to date, we have scarce literature on COVID-19 symptoms associated with the nervous system.

COVID-19 has killed millions across the world and has affected every nation, every individual on this planet, directly or indirectly, by causing a spectrum of disorders oscillating from no symptoms to death and indirectly by resulting in sickness or loss of a family member or socioeconomic turbulence due to restricted services, movement of people and goods, inflation, stock market collapse, declining GDP and grief and increasing mental stress.[8] Initially only respiratory symptoms were reported due to SARS-CoV-2 infection but thereafter several non-respiratory features have been observed, including neurological deficits. Contemporary literature has shown that neurological symptoms were found in 84% of the patients that entered the intensive care unit without sedation and neuromuscular blockers. They expressed CNS dysfunction symptoms such as agitation (69%) and confusion (65%).[9] A systematic review showed that 23% of the patients also had complications of encephalopathy or encephalitis.[10] These results have indicated the possibility of central nervous system involvement in the course of COVID-19 disease, with the presence of SARS-CoV-2 neurotropism.[11] Several other reports also suggest that various neurologic sequelae may arise in association with respiratory coronavirus syndromes, including encephalitis, seizures, encephalopathy, Guillain-Barre syndrome (GBS), anosmia, enteropathy, neuromuscular disorders, and demyelinating diseases.[10–13] Similarly, the neurotropism of other types of human coronaviruses (including HCoV-229E, HCoV-OC43, HCoVHKU1, and HCoV-NL63) and their possible association with neurologic diseases such as multiple sclerosis (MS) have been debated in earlier studies.[14,15]

A very recent review has found that myalgia, anosmia, headache, cerebrovascular disease, and encephalopathy are amongst the most common neurological manifestations associated with SARS-CoV-2 infection.[16] Neurological features such as weakness, pain, and numbness are reported readily as they are easily noticed by the patients. Direct neural invasion, neuroinflammation, systemic pro-inflammatory state, and hypoxia have all been suggested to mediate the neurological dysfunction in COVID-19.[17] Thus, indicating a direct pathophysiological basis to the neurological features.

SARS-CoV-2 virus can cross the blood-brain barrier, most probably, the virus travels to the brain by a hematogenous route or trans-neuronally to the brain via the olfactory system, across cribriform plate.[18] Angiotensin-converting enzyme-2 (ACE-2) receptor's role in virus binding is well known and their presence on endothelial cells of cerebral vasculature act as entry points for the virus[19]. In an autopsy-based study, it was demonstrated that the SARS-CoV-2 virus is present in neural and capillary endothelial cells of the frontal lobe of the brain. Neurons or microglia did not have angiotensin-converting enzyme two receptors.[20] Comorbidities, like diabetes and hypertension, enhance the angiotensin-converting enzyme 2 receptor expression in the brain and in turn, increase neurotropism of the SARS-CoV-2 virus.[21] The SARS-CoV-2 virus epitopes bear a structural resemblance to several human proteins. Hence, molecular mimicry between virus epitope and myelin basic protein results in auto-immune post-infectious demyelinating syndromes.[22] Dysregulation of the angiotensin-converting enzyme-2 receptor also contributes to the pathogenesis of experimental autoimmune encephalomyelitis.[23,24] Spike surface glycoprotein plays a crucial role in immunopathology. Delirium is often associated with systemic inflammation and prolonged hypoxia. Middle-aged and older adults with severe disease are more likely to be affected.[25] Altered sensorium, in COVID-19, is associated with an increased risk of death.[26] Xiang and co-workers, in Beijing, China, claimed to isolate the first SARS-CoV-2 virus in cerebrospinal fluid (CSF).[27] In only a handful of patients, the SARS-CoV-2 virus in CSF has been isolated. In a case of COVID-19 associated encephalitis, MRI revealed the involvement of brain parenchyma. Patients also presented with corticosteroid-responsive encephalopathy, acute disseminated encephalomyelitis, and immune-mediated acute hemorrhagic necrotizing encephalopathy.[28–31]

Severe COVID-19 is characterized by profound coagulopathy. In patients of severe COVID-19, coagulopathies are important detrimental factors that are invariably associated with poorer outcomes. The hallmark coagulopathy abnormalities in COVID-19 are raised prothrombin time (PT), raised D-dimer level, and mild thrombocytopenia, but without hypofibrinogenemia. DIC is characterized by thrombocytopenia, prolonged PT, and markedly elevated D-dimer.[32,33] Coagulopathies in COVID-19 predispose to stroke and other prothrombotic events.[34–36] Severe COVID-19 is also characterized by markedly elevated levels of pro-inflammatory cytokines, lymphopenia, increased number of neutrophils collectively termed as "cytokine storm", approximately, 5% of COVID-19 patients develop acute respiratory distress syndrome (ARDS), septic shock, and/or multiple organ dysfunctions (MODS). A cytokine storm is held responsible for the pathogenesis of all the complications of severe COVID-19.[37,38] The SARS-CoV-2 virus infection can trigger hemophagocytic lympho-histiocytosis (HLH), which is a rare hyperinflammatory condition characterized by a severe hyper-cytokinaemia with multiorgan failure.[39,40] Recently even "bradykinin storm" has been proposed as a phenomenon well observed in severe COVID-19[41].

Thus, the author here wants to highlight two interesting cases which presented with non-specific neurological

symptoms and turned out to be primarily COVID-19 positive with meningo-enchephalitis.

2. Case Study

2.1. Case 1

A 19 years old male was brought by his colleagues to the Emergency Room in agitated condition, not responding to verbal commands for the past few hours and having high-grade fever for past few hours. There was a history of headache and insomnia for past 02 days. No other relevant history and symptoms. No known comorbidities. There was no history of recent travel or trauma. No signs and symptoms of upper and lower respiratory symptoms.

2.1.1. On initial examination vital parameters were

Blood Pressure – 120/70 mmHg, Pulse Rate – 110/min, Temperature – 104 Degree Fahrenheit, SpO2 – 98% on room air.

2.1.2. Systemic examination revealed

Respiratory system – Bilateral normal vesicular breath sounds, no wheeze / crepitations heard.

Cardiovascular system – S1S2 heard normally, no murmurs / splits heard.

Per-abdominal system – Soft, non-tender, no organomegaly, bowel sounds heard normally.

Neurological system – Pupils were bilaterally reacting to light equally, moving all four limbs, agitated and not responding to verbal commands. Responds to pain. No apparent motor deficit.

2.2. Case 2

A 46 years old female brought by her relatives to the Emergency Room in confused and delirious condition, not responding to verbal communication from past few hours and having low grade fever since last 01 day. There was history of myalgia, headache and insomnia from past 02 days. K/c/o HTN and arthritis, on medication. No other relevant history and symptoms. There was no history of recent travel or trauma. No signs and symptoms of upper and lower respiratory symptoms.

2.2.1. On initial examination vital parameters were

Blood Pressure – 130/80 mmHg, Pulse Rate – 100/min, Temperature – 101 Degree Fahrenheit, SpO2 – 97% on room air.

2.2.2. Systemic examination revealed

Respiratory system – Bilateral normal vesicular breath sounds, no wheeze / crepitations heard.

Cardiovascular system – S1S2 heard normally, no murmurs / splits heard.

Per-abdominal system – Soft, non-tender, no organomegaly, bowel sounds heard normally.

Neurological system – Pupils were bilaterally reacting to light equally, moving all four limbs, delirious and not responding to verbal commands. Responds to pain. No apparent motor deficit.

2.2.3. Diagnosis

In both cases, a diagnosis of COVID Associated MENINGO-ENCEPHALITIS was made.

2.2.4. Management

Patients were managed with steroids and a single dose of Inj. Tocilizumab, to which they responded well and became asymptomatic within 02 weeks of intensive care at ICU and were discharged to home with directions to follow National guidelines regarding Home Quarantine for the period of convalescence.

3. Discussion

The above cases clearly demonstrate the levels of subtleness in the symptomatic presentations of neurological involvement of COVID-19. Although the main target of organ damage by SARS-CoV-2 has been the respiratory system, patients have also experienced neurological problems ranging from the mild manifestations (headaches and dizziness) to life-threatening complications (cerebrovascular disorders and encephalitis). Current literature shows that agitation (69%) was the common complaint found in COVID-19 patients receiving treatment in the Intensive Care Unit (ICU).[42] In our cases, fever, headache, insomnia with agitation and confusion were the primary symptoms. Recent publications have also proved this atypical presentation of COVID-19. Based on current studies, the common symptoms found in most of the common causes of acute viral encephalitis patients are disorientation or confusion (72.72%), decreased consciousness (54.54%), and seizures (27.27%). These symptoms indicate damages in the central nervous system, especially the cerebral cortex, typically found in acute encephalitis. In COVID-19 associated encephalitis, the manifestations of seizures and headaches are found in 27.27% and 30.3% of the cases, while HSV encephalitis seizures are found in 56% of the cases and headaches in 83% of the cases.[43] Abnormal behaviour that is characteristically found in HSV is rarely found in COVID-19 associated encephalitis. The clinical appearance of COVID-19 associated encephalitis is parallel to MERS-CoV-2 associated encephalitis, like symptoms of upper respiratory tract infection (fever, cough, fatigue, etc.), a decrease in mental status and rapid respiratory failure.[43] Meningeal irritation sign has not been classically found in this association, which suggests that the pathological process is more dominant in the cortex than in the meninges.

Table 1: Investigations

S.No.	Investigation	Reports Case-1	Reports Case-2
Haematology			
1.	Hb	14 gm%	11.4 gm%
2.	TLC	9100/ul	8600/ul
3.	DLC	Neutrophils- 89%, Lymphocytes- 08%, Monocytes- 02%, Eosinophils- 01%, Basophils- 00%	Neutrophils- 71%, Lymphocytes- 18%, Monocytes- 03%, Eosinophils- 08%, Basophils- 00%
4.	PT Patient	16	15
5.	PT Control	13	13
6.	INR	1.1	1.1
7.	PTTK Patient	35	–
8.	PTTK Control	32	–
9.	MP Paracheck	Negative	Negative
10.	PBS for MP	No Malarial Parasite seen	No Malarial Parasite seen
11.	Dengue IgG/IgM/NS1Ag	Negative	Negative
Serology			
1.	Ferritin (Vidas)	156.91 ng/ml	169.23 ng/ml
2.	Procalcitonin (Vidas)	0.05 ng/ml	0.09 ng/ml
3.	D-Dimer (Vidas)	2913.87 ng/ml of FEU	2801.66 ng/ml of FEU
4.	CRP	Negative	Raised
Biochemistry			
1.	Calcium	Albumin Calcium – 3.8 gm/dl; Calcium 2 – 7.9 mg/dl	
2.	Blood Sugar	Fasting – 102 mg/dl; Post Prandial – 148 mg/dl; Random Blood Sugar – 118 mg/dl	Random Blood Sugar – 126 mg/dl Fasting – 92 mg/dl PP – 168 mg/dl
3.	Urea	18 mg/dl	32 mg/dl
4.	Creatinine	0.6 mg/dl	0.8 mg/dl
5.	Uric Acid	4.8 mg/dl	6.2 mg/dl
6.	Albumin	3.8 gm/dl	3.7 gm/dl
7.	Proteins	6.5 gm/dl	5.7 gm/dl
8.	Globulin	2.7 gm/dl	2.0 gm/dl
9.	AG Ratio	1.4	1.9
10.	Bilirubin	Total – 1.4 mg/dl; Direct – 0.3 mg/dl	T – 1.0 mg/dl; Direct – 0.3 mg/dl
11.	SGOT/AST	83 IU/L	100 IU/L
12.	SGPT/ALT	43 IU/L	56 IU/L
13.	ALP	108 IU/L	70 IU/L
14.	LDH	515 IU/L	300 IU/L
15.	Sodium	135 meq/dl	136 meq/dl

Continued on next page

Table 1 continued

16.	Potassium	3.0 meq/dl	3.4 meq/dl
CSF Cytology			
1.	Appearance	Clear	Clear
2.	Volume	02 ml	01 ml
3.	Reaction	Alkaline	Alkaline
4.	RBCs	Nil	Nil
5.	WBCs	7/cmm	10/cmm
6.	Predominant Cells	Lymphocytes	Lymphocytes
CSF Biochemistry			
1.	CSF Glucose	79 mg/dl	82 mg/dl
2.	CSF Protein	62.2 mg/dl	66 mg/dl
3.	CSF Globulin	Not Increased	Not raised
4.	CSF ADA	2.2 IU/L	2.8 IU/L
CSF Microbiology			
1.	CSF Culture	No Growth seen after 48 hours	No Growth seen after 48 hours
2.	CSF Gram Stain	Negative	Negative
3.	CSF ZN Stain	Negative	Negative
4.	CSF India Ink Preparation	Negative	Negative
	Chest X-Ray	Normal	Normal
	NCCT Chest and Brain	Normal	Normal
	MRI Brain	Hyperintense focal areas in left posterior-parietal lobe and parieto-occipital lobe, wall of frontal parietal lobe, cortical and sub-cortical areas. Meningeal enhancement seen. Suggestive of Meningoenchephalitis.	Non confluent multifocal white matter hyper intense lesions seen with signal abnormalities located in medial temporal lobe. Occasional isolated microhemorrhages noted along with meningeal enhancement. Indicative of Meningoenchephalitis
	COVID19 Testing	CBNAAT Positive	CBNAAT Positive
	HSV PCR	Negative	Negative

This also indicates that the involvement of meninges in COVID-19-associated encephalitis is less common than HSV[44]. Same has been found in our cases. Though largely COVID-19 patients have shown a normal magnetic resonance imaging (MRI) images, the most common radio-pathological finding in most of the current studies has been diffuse hyper-intensity of T2 / Fluid attenuated inversion recovery (FLAIR), with location most frequently in white matter which was the chief finding in our cases too. A case series of three cases of middle east reported respiratory syndrome coronavirus (MERS-CoV) patients that evaluation by MRI showed hyper-intense lesions on T2, spread widely and bilaterally in white matter and subcortical areas, frontal lobes, temporal, parietal, and basal ganglia, as well as the corpus callosum.[45] Thus, the neuroimaging findings suggest possible similarities in the pathological mechanism of the central nervous system involvement in SARS-CoV- 2, SARS-CoV, and MERS-CoV, which was the common finding in our cases also. The CSF analysis of our cases showed slightly raised number of white blood cells with lymphocyte predominance, and raised levels of CSF proteins, which has been the finding in many contemporary studies and case series, showing increase in protein levels (42.42%), white blood cells (WBCs) (27.27%), and lymphocytes (24.24%). In addition, most of the case series have also reported that the cerebrospinal fluid (CSF) and polymerase chain reaction (PCR) examination with a negative result for SARS-CoV-2, due to the direct invasion of the virus into white matter.[44–49] Our cases were not subjected for CSF SARS-CoV-2 analysis as enough evidence has been published directly associating SARS-CoV-2 with Meningo-enchephalitis as CSF tested positive for SARS-CoV-2 RNA also there is evidence of associated intracerebral micro-hemorrhages of medial temporal lobe as seen in our case.[50]

4. Conclusion

Patients with atypical neurological presentations during the COVID pandemic need a strong suspicion towards COVID-associated CNS symptoms. CNS infection by SARS-CoV-2 has been seen to result in severe COVID disease if not managed aggressively. MRI brain forms a mainstay modality in these atypical CNS cases. All flu-like cases even with atypical presentations need to be subjected to COVID-19 testing.

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6. Conflict of Interest

The authors declare that there is no conflict of interest.

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