COVID-19 associated meningoencephalitis complicated with intracranial hemorrhage. A case report.

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Abstract

Introduction: The Coronavirus pandemic that started in December 2019 is mainly related to clinical pictures consistent with respiratory symptoms; nevertheless, reports about neurological complications have recently appeared in the medical literature.

The case: we describe a case of a 36 years old Coronavirus-positive patient that was admitted on emergency basis; his clinical presentation included neurological symptoms such as drowsiness and mild confusion. Imaging revealed findings consistent with meningoencephalitis complicated by intracerebral hematoma and subdural hematoma. The latter was surgically evacuated after it became chronic and evidence of Coronavirus was found in the fluid.

Conclusion: our experience confirms that neurological complications might be a likely event in COVID-19. Although uncommon, the possible occurrence of meningoencephalitis should be kept in mind by physicians involved in the management of COVID-19 patients. Early recognition of brain involvement may provide better prognosis, preventing evolution into intracerebral hemorrhagic events.

Introduction

Coronavirus disease 2019 (COVID-19) started in December 2019 and about 3.8 million confirmed cases and more than 260,000 deaths have been reported worldwide until present date. Although the typical clinical picture is mainly related to the respiratory system and usually includes symptoms as fever, shortness of breath and cough, there is ongoing evidence that other body systems might be affected. Neurological manifestations have also been reported[1,2,6,7,13]; a case of COVID-19–associated acute necrotizing hemorrhagic encephalopathy was recently published [9].

We describe a case of COVID-19–associated meningoencephalitis complicated with intracerebral hemorrhage and subdural hematoma.

Case Report

A 36 years old male patient presented to one of the peripheral healthcare centers on 15/4/2020 with two days history of fever, headache, body pain, cough, diarrhea and vomiting. On physical examination, pharyngitis only was found. Blood tests showed normal full blood count. The patient was submitted to NOVEL CORONAVIRUS RNA PCR swab that resulted negative. He was diagnosed as gastroenteritis and discharged.

On 19/4/2020, the patient visited the emergency department of a central hospital as he was still complaining of the same symptoms; additionally, he presented drowsiness and appeared mildly confused. The patient denied head trauma or seizure.

On examination, Glasgow Coma Scale (GCS) scored 13/15; the patient was drowsy but arousable, he showed mild confusion although he was still oriented to time and place. Pupils were isochoric (3 mm diameter) and reactive. Cranial nerves were normal. He presented no signs of trauma, no overt weakness, no nuchal rigidity (mild stiffness) or pain while moving the neck.

Blood tests (Table 1-4) showed high WBC count 12.9 10^3/uL; CRP was normal, Procaltitonin was high 0.10 ng/mL, D-Dimer high 0.79 ug/ml FEU. Random Glucose was high 165 mg/d.

NOVEL CORONAVIRUS RNA PCR swab was repeated and resulted positive.
Chest x-ray was performed and did not show any pathological findings.

Based on neurological examination, the patient was investigated with Brain CT (Figure 1). The study showed a right frontal intracerebral hematoma associated with subarachnoid hemorrhage in the ipsilateral sylvian fissure, frontal and temporal lobes; a thin, acute subdural hematoma was also evident. The hematoma appeared surrounded by edema and caused midline shift. The radiologist attributed the described findings to encephalitis and viral etiology was suspected.

Diagnostic workup was completed with CT-angio on the same day (Figure 2a and 2b). The investigation did not show any arteriovenous malformation or aneurysms, it also ruled out the possibility of venous thrombosis. Bilateral supratentorial leptomeningeal increased enhancement was detected and further supported the diagnosis of COVID-19 related meningoencephalitis (Figure 3a and 3b).

The evidence of midline shift on the CT scans contraindicated a lumbar puncture to assess the presence of Coronavirus in the CSF.

MRI could not be performed as in our facility it is not allowed for COVID 19 patients.

EEG was also ruled out to prevent further exposure with the COVID-19 patient and because CT and CTA were reckoned conclusive

The patient was admitted to the ICU with close neuro-observation. He remained stable and several chest x-rays were all normal.

On 2/5/2020, the patient was still neurologically stable (GCS 14/15) yet on brain CT- follow up (Figure 4), the right subdural hematoma had become chronic, the intracerebral hematoma was re-reabsorbing with persistent perilesional brain oedema and midline shift. Based on radiological findings, indication for surgery was advocated; evacuation of the chronic subdural hematoma was performed on 5/5 via burr hole. The fluid from the chronic subdural hematoma was sent for PCR. Novel Coronavirus RNA PCR-fluid (CSF) was positive.

**Discussion**

Severe acute respiratory syndrome-coronavirus (SARS-CoV) is well known to affect the nervous system and induce polyneuropathy, encephalitis and aortic ischemic stroke[11,12]; its presence has been found in CSF [3] and brain parenchyma in autopsies [14].

SARS-CoV has more than 80 % genetic similarity to SARS-Cov2[4,8], the virus responsible of COVID-19. Recent clinical data revealed that COVID-19 patients could manifest symptoms such as headache, epilepsy and disturbed conscious level suggestive of intracranial infections[1,6]. Others had anosmia and dysgeusia [2,7,10,15]. Reports of COVID-19 encephalitis[6] and a case of COVID-19–associated acute hemorrhagic necrotizing encephalopathy[7] have been recently published in the medical literature. The presence of Coronavirus was found in CSF, hence confirming that the neurological complications observed in these patients are to be attributed to the virus.

Several hypothesis have been advocated to explain neurological complications in COVID 19. Coronavirus is able to bind Angiotensin-converting enzyme 2 (ACE2) [2], known to regulate blood pressure and to play an anti-atherosclerosis mechanism; ACE2 is present in the nervous system among other organs. The Coronavirus–ACE 2 binding is responsible of direct damage to the blood-brain-barrier (BBB); moreover, since on systemic level, it may result in elevating blood pressure, it predisposes to the occurrence of cerebral hemorrhage.

Another explanation might involve the cytokine cascade. Accumulating evidence has suggested that in a subgroup of patients with severe COVID-19, a secondary haemophagocytic lymphohistiocytosis (sHLH) may develop; this results in a hyperinflammatory syndrome characterised by a fulminant and fatal hypercytokinaemia with multiorgan failure [5]. Experimentally, it has been demonstrated that the cytokine cascade could cause intracerebral hemorrhage[7]. COVID-19-induced cytokine storm syndrome could be
another of the factors behind the occurrence of cerebrovascular events.

The virus seems to have neurotropic properties and may access the CNS through the olfactory nerve; this neuronal pathway is consistent with the clinical observation that some patients with COVID-29 develop anosmia[2,7,10,15].

Our case report gives further evidence of neurological complications in COVID 19. We illustrated the case of a Coronavirus- positive 36 year old patient with unremarkable past medical history that developed a meningoencephalitis with intracerebral and subdural hematomas. On admission, the patient had not been able to report about possible anosmia or dysgeneusia due to his state of confusion. Nevertheless, in spite of the contraindication to perform lumbar puncture to detect the presence of the virus in CSF, we had considered the coronavirus infection as the only possible etiology from early diagnostic assessment. Clinical and radiological data were indeed considered suggestive of this etiology; the patient had no history or physical/radiological evidence of head trauma, imaging had ruled out the possibility of vascular abnormalities and showed findings certainly consistent with viral infection. Later on, our clinical suspicion was eventually confirmed by the analysis of the fluid obtained from the surgical evacuation of the chronic subdural hematoma.

**Conclusion**

It has been previously demonstrated that COVID-19 can cause encephalitis and even result in hemorrhagic encephalopathy. Albeit rare, the possibility of neurological complications should be always kept in mind by physicians involved in the diagnosis and management of COVID-19 cases; even in absence of anosmia/dysgeneusia, symptoms like altered conscious level, headache and sensory-motor deficits should raise a red flag, prompting to investigations that might detect the occurrence of a possible brain damage.

Early diagnosis of encephalomyelitis by imaging is crucial to offer appropriate treatment and prevent evolution towards hemorrhagic encephalopathy, a complication that may cause severe invalidity or even threaten the patient’s life.

**Declarations**

**Conflict of Interest:**

The authors declare that they have no conflict of interest.

**Patient Consent:**

The IRB board of the (Dubai Health Authority - Dubai Scientific Research Ethics Committee) waived patient consent for this case report submission.

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### Tables

#### Coagulation Profile

| Test               | Result   |
|--------------------|----------|
| Prothrombin Time   | 11 - 14 Secs |
| Prothrombin Time Ratio | 0.9   |
| INR                | 0.8 - 1.1 |
| PT Control         | 0.9   |
| APTT               | 28 - 41 Secs |

*Table 1 (Coagulation Profile)*
### Lever function test

| Test               | Normal Range | Value   |
|--------------------|--------------|---------|
| Bilirubin, Total   | 0 - 1.0 mg/dL| 0.3     |
| Alkaline Phosphatase| 40 - 129 U/L | 108     |
| SGPT(ALT)          | 0 - 41 U/L   | 196     |
| Total Protein      | 6.6 - 8.7 g/dL| 7.4     |
| Albumin            | 3.4 - 4.8 g/dL| 3.6     |
| Globulin           | 2.8 - 3.4 g/dL| 3.8     |

*Table 2 (Lever function test)*

### G6PD

- **G-6PD Screen**: Normal
- **G6PD QUANTITATIVE**: 146 - 376 u/10^12 RBC

*Table 3 (G6PD test)*

### Respiratory Screening Panel PCR Nasopharynx

| Test                  | Ref Range & Units | 2d ago                      |
|-----------------------|-------------------|-----------------------------|
| Influenza A PCR       | Not detected (Negative) | Not detected (Negative) |
| Influenza B PCR       | Not detected (Negative) | Not detected (Negative) |
| Para Influenza 1 PCR  | Not detected (Negative) | Not detected (Negative) |
| Para Influenza 2 PCR  | Not detected (Negative) | Not detected (Negative) |
| Para Influenza 3 PCR  | Not detected (Negative) | Not detected (Negative) |
| Para Influenza 4 PCR  | Not detected (Negative) | Not detected (Negative) |
| Bordetella Pertussis PCR | Not detected (Negative) | Not detected (Negative) |
| Mycoplasma pneumoniae PCR | Not detected (Negative) | Not detected (Negative) |
| Enterovirus/Rhinovirus PCR | Not detected (Negative) | Not detected (Negative) |
| Influenza A subtype H1N1/2009 PCR | Not detected (Negative) | Not detected (Negative) |
| Influenza A subtype H1 PCR | Not detected (Negative) | Not detected (Negative) |
| Influenza A subtype H3 PCR | Not detected (Negative) | Not detected (Negative) |
| Coronavirus 229E PCR | Not detected (Negative) | Not detected (Negative) |
| Coronavirus HKU1 PCR  | Not detected (Negative) | Not detected (Negative) |
| Coronavirus NL63 PCR  | Not detected (Negative) | Not detected (Negative) |
| Coronavirus OC43 PCR  | Not detected (Negative) | Not detected (Negative) |
| Respiratory Syncytial virus A + B PCR | Not detected (Negative) | Not detected (Negative) |
| Human Metapneumovirus A + B PCR | Not detected (Negative) | Not detected (Negative) |
| Adenovirus PCR        | Not detected (Negative) | Not detected (Negative) |
| CHLAMYDIA PNEUMONIAE | Not detected (Negative) | Not detected (Negative) |
| MERS CORONAVIRUS      | Not detected (Negative) | Not detected (Negative) |

Comment: This panel does not detect MERS Corona Virus and 2019 Novel Corona Virus

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**BORDETELLA PARAPERTUSSIS**: Not detected (Negative) | Not detected (Negative)
Figure 1

Non-enhanced CT Brain Axial cut showing a large parenchymal hematoma in the right frontal lobe with surrounding edema. Extracerebral hemorrhage is also observed subdural as well as subarachnoid. Note the cortical swelling evident as loss of demarcation of grey-white matter interface and effacement of sulci in temporo-occipital region on the right side and frontal lobe on the left.
Figure 2

a: Coronal MIP: CTA findings show reduced and somewhat beaded appearance of the distal ICA, A1 and M1 and M2 branches on the right side reflecting vasospasm/vasculitis. b: Axial MIP: CTA findings show reduced and somewhat beaded appearance of the distal ICA, A1 and M1 and M2 branches on the right side reflecting vasospasm/vasculitis.
Figure 3

a: Delayed post contrast imaging shows Leptomeningeal as well as cortical gyral enhancement supratentorially bilaterally, more pronounced on the right side. The findings strongly suggestive of meningo-encephalitis. b: Delayed post contrast imaging shows Leptomeningeal as well as cortical gyral enhancement supratentorially bilaterally, more pronounced on the right side. The findings strongly suggestive of meningo-encephalitis.
Follow up imaging shows reduced attenuation of the SDH and good resorption of SAH. The intracerebral hematoma shows signs of partial resorption but mild increase of perifocal oedema. No significant interval change of mass effect in the form of effaced sulci and midline shift of about 10 mm.