ORIGINAL ARTICLE

Hemorrhagic stroke associated to COVID-19 infection in Mexico General Hospital

Accidente cerebrovascular hemorrágico asociado a infección por COVID-19 en Hospital General de México

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Abstract

Introduction: *In the current COVID-19 pandemic, there is a growing body of evidence that has identified the neurotropism of the SARS-CoV-2 virus and its neurological complications, including cerebrovascular disease, focusing mainly in ischemic and scarcely about hemorrhagic stroke (HS).* **Objective:** *The objective of the study was to describe clinical, radiological, laboratory tests, and prognostic characteristics of patients with SARS-CoV-2 associated HS.* **Methods:** *Consecutive patients with a confirmatory PCR test for SARS-CoV-2 infection and a HS demonstrated by head CT were included in the study.* **Results:** *Over a period of 90 days, in a COVID-19 reference center in Mexico, out of a total of 1108 patients with SARS-CoV-2 infection, it found 4 patients (0.36%) who meet criteria. They had an age of 71 (±12.2) years, 2 were women. It was found that two had prior cardiovascular risk factors. Two of the HS originated in the dentate nucleus while the other two corresponded to the thalamus. Three of the four patients died. We suggest that catastrophic uncontrolled blood pressure, coagulopathy, thrombocytopenia, and immune response induced by SARS-CoV-2 could in a specific patient trigger HS.* **Conclusions:** *HS is associated to SARS-CoV-2 infection with poor prognosis when it presented. Neurosurgery teams should prepare for the timely and appropriate treatment of this patients.*

Key words: *Cerebrovascular disease. Coagulopathy. COVID-19. Hemorrhagic stroke. SARS-CoV-2 infection.*

Resumen

Introducción*: en la actual pandemia de COVID-19, existe evidencia creciente que ha identificado el neurotropismo del virus SARS-CoV-2 y sus complicaciones neurológicas, incluida la enfermedad cerebrovascular isquémica y escasamente hemorragia cerebral (HC).* **Objetivo:** *describir las características clínicas, radiológicas, de laboratorio y pronósticas de los pacientes con HC asociada al SARS-CoV-2.* **Métodos:** *se incluyeron pacientes consecutivos con prueba de PCR confirmatoria para infección por SARS-CoV-2 y HC.* **Resultados:** *en un período de 90 días, en un centro de referencia COVID-19 en México, de 1108 pacientes con infección por SARS-CoV-2, se encontraron 4 pacientes (0.36%) con HC. Tenían una edad de 71(±12.2) años, 2 eran mujeres. Se encontró que dos tenían factores de riesgo cardiovascular previos. En dos casos se encontró el origen en el núcleo dentado mientras que los otros dos correspondieron al tálamo. Tres de los cuatro pacientes murieron. Postulamos que el descontrol hipertensivo, coagulopatía, trombocitopenia y la respuesta inmune inducida por el virus SARS-CoV-2 podrían desencadenar HC en un paciente con riesgo previo.* **Conclusiones:** *la HC se asocia a la infección por SARS-CoV-2 con mal*

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pronóstico cuando se presenta. Los equipos de neurocirugía deben estar preparados para el tratamiento oportuno de estos pacientes.

Palabras clave: *Enfermedad cerebrovascular. Coagulopatía. COVID-19. Hemorragia cerebral. SARS-CoV-2.*

Introduction

Hemorrhagic stroke (HS) is one of the most frequent pathologies in routine neurosurgical practice, with well-known cardiovascular risk factors, clinical presentation, and prognosis[1]. By December 2019, a series of patients with atypical pneumonia were identified in Wuhan, China, which would eventually become the SARS-CoV-2 pandemic. As of the end of December 2020, more than 80,000,000 cases and more than 1,450,000 deaths had been identified worldwide, being Mexico one of the most affected countries in the Americas region[2]. The typical symptoms of COVID-19 at illness onset are dry cough, fever, and dyspnea with abnormal CT chest examinations and pulmonary complications such as septic shock and acute respiratory distress syndrome (ARDS)[3]. However, in the current COVID-19 pandemic, there is a growing body of evidence that has identified neurological manifestations in 36.4-57.4% of patients including anosmia, dysgeusia, disorders of consciousness, epilepsy, and cerebrovascular diseases focusing mainly in ischemic and scarcely about hemorrhagic stroke[4-6]. The neurotropism of the SARS-CoV-2 virus was primarily suspected due to the similarity of its structure with other disease-causing coronaviruses such as MERS and SARS and posteriorly by direct identification in postmortem examinations[7-10].

From a neurosurgical point of view, being aware of HS as a probable complication, knowing its presumed pathophysiology, and being prepared for its treatment are crucial to maintain a quality standard of care in these patients, while at the same time prevent infection spread to the neurosurgical team. In this report, we present the clinical, laboratory tests, radiological, and prognostic characteristics of four patients with SARS-CoV-2 infection who have an associated HS in a reference hospital for COVID-19 in Mexico.

Patients and methods

A descriptive clinical study with retrospective analysis of HS cases at "*General Hospital of Mexico*" (GHM) during the current COVID-19 pandemic was conducted. The GHM is a tertiary referral hospital in Mexico City, and it was designated for priority care of patients with SARS-CoV-2 infection. From March 23 to June 20, 1108 patients with COVID-19 had been hospitalized. During this period, the neurosurgery department was assigned to urgent neurosurgical procedures and to solve potential neurosurgical complications for COVID-19 patients. We included 4 patients (0.36%) with confirmatory nasopharyngeal RT-PCR test for SARS-CoV-2 and who had evidence by CT scan of the skull of HS during their hospitalization (Table 1). For the purposes of this report, it was obtained demographic data, clinical characteristics, laboratory, and image results of the patients, as well as their evolution. It was described each case with percentages, simple frequencies, and measures of central tendency with average and dispersion measures with standard deviation. Before the entrance to the hospital, each patient/relative signed an informed consent to his treatment. During the elaboration of this report, the patients' confidentiality was preserved, and it was carried out in accordance with the ethical principles of the Helsinki Declaration.

Results

Case 1

A 77-year-old female presented 5 days before admission, with symptoms of respiratory distress and tachypnea. The patient had a history of hypertension and type 2 diabetes mellitus (DM2), without further cardiovascular risk factors. On hospital admission, presenting desaturation. On hospital admission, presenting desaturation, also clinic and laboratory compatible with severe pneumonia due to probable SARS-CoV-2. High-resolution chest tomography was performed showing basal consolidation predominantly on the left lobe. She presented 24 h after admission a neurological impairment characterized by decreased alertness, incoherent language, followed by response to the painful stimulus only, associated with a hypertensive crisis, as well as depletion of respiratory function. Confirmatory RT-PCR test for COVID-19 infection was requested. A simple brain CT scan was performed in which the presence of predominantly left cerebellar hemorrhage was observed, with disruption to infra- and supratentorial

Table 1. Characteristics of patients with HS associated to SARS-CoV-2 infection

Case N° (Age/ Gen)	SARS-CoV-2 involvement	Vascular risk factors	Clinical presentation	Blood pressure at admission	Localization of the hemorrhage	Abnormal blood test	Treatment	Outcome
1 (77/F)	Severe	Hypertension DM2	GCS 9 points, decreased alertness, incoherent language.	160/90 mmHg	Left dentate nucleus with ventricular disruption.	CRP (133 mg/L), PCT (2.35 ng/ml), CPK-MB (313 u/L), myoglobin (21.4 ng/ml) ↑D-Dimer (1452 ug/L), ↑INR (1.8), ↑fibrinogen (1452 mg/ dL), LDH (278 U/L).	Ceftriaxone Acetaminophen Enoxaparin	Death
2 (67/M)	Severe	None	GCS 3 points, headache decreased alertness.	90/60 mmHg	Left dentate nucleus with ventricular disruption.	↑Ferritin (999 ng/ml), ↑CRP (422 mg/L), CPK-MB (673 u/L) ↑ LDH (469 U/L), ↑D- Dimer (4114 ug/L), ↑fibrinogen (975 mg/dL).	Ceftriaxone Azithromycin Acetaminophen Dexamethasone Enoxaparin	Death
3 (56/M)	Moderate	Hypertension DM2	GCS 14 points, left hemiparesis, hemi-hypoesthesia, hyperalgesia, and ipsilateral allodynia	140/90 mmHg	Right thalamus with ventricular disruption.	Kidney failure (Cr 2.18 mg/dL), ↑Ferritin (556 ng/ml) ↑LDH (293 U/L), ↑fibrinogen (512 mg/dL). ↓Platelets (114,000)	Azithromycin Acetaminophen Methylprednisolone	Death
4 (84/F)	Mild	None	GCS 13 points, right hemiparesis.	125/80 mmHg	Left thalamus with extension to basal ganglia.	↑CRP (16.3 mg/L), ↑D-Dimer (4476 ug/L), ↑Fibrinogen (413 mg/dL) ↓Platelets (110,000)	Acetaminophen	Discharged GOS 5

CRP: C-reactive protein; CPK-MB: creatine kinase; GCS: glasgow coma scale; LDH: lactate dehydrogenase; PCT: procalcitonin.

ventricular system, hydrocephalus, and sealed subarachnoid space. During assessment by neurosurgery, 30 h after admission, the patient was intubated and under pharmacological sedation, with clinical signs of brain death. Laboratory blood tests showed increased INR (1.8) and D-dimer (1452 ug/L); elevated cardiac enzymes CPK-MB (313 u/L), myoglobin (251.4 ng/ml), LDH (278 U/L), and acute-phase reactants. The patient was considered out of surgical treatment. The patient dies the day after our evaluation (Fig. 1).

Case 2

A 67-year-old male without chronic diseases began 10 days prior admission to our hospital, when he presented non-productive cough, intense headache, myalgias, arthralgias, and diaphoresis predominantly at night. His condition began 10 days prior admission to our hospital, when he presented non-productive cough, intense headache, myalgias, arthralgias, and diaphoresis predominantly at night. No other main neurological symptoms were presented. Four days later, he progressed with thermal rises and respiratory distress. He was taken to the emergency room (ER) in poor general condition, requiring advanced management of airway. He was admitted in the intensive care unit (ICU) with a diagnosis of severe pneumonia. A RT-PCR test for SARS-CoV-2 was requested resulting positive. During hospitalization, he developed acute renal failure, elevation of the liver enzymes (total bilirubin 3.10 mg/dL), and GGT (1040 U/L), ferritin (999 ng/ml), cardiac enzymes (CPK 673 u/L and myoglobin 139 ng/ml), LDH (469 U/L), CRP (422 mg/L), as well as increased fibrinogen (975 mg/dL) and D-dimer (4114 ug/L). Chest X-ray demonstrated bilateral ground-glass opacities and a right basal condensation. No chest CT was performed. He was maintained with pharmacological measures, as well as anticoagulation prophylaxis (enoxaparin 1 mg/kg). He presented slight improvement of the ventilatory function, for this reason, withdrawal of sedation was decided, without neurological response. A simple brain CT was requested, showing left cerebellar hemorrhage, with extension through the pons and the ipsilateral occipital lobe, infra- and supratentorial ventricular disruption, hydrocephalus, and brainstem infarction. Neurosurgical

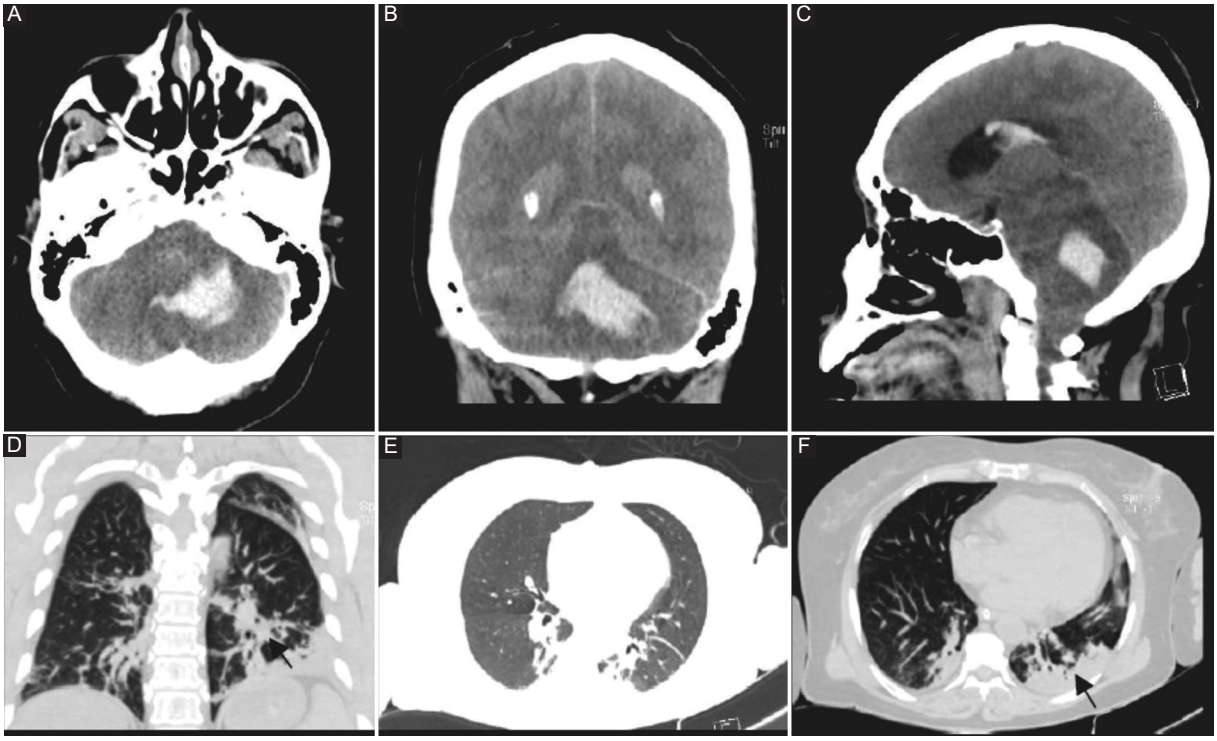

Figure 1. A-F: *chest and brain CT examination of patient 1.* **A-C:** *multiplanar brain CT reconstruction showing presence of the left cerebellar hemorrhage, compromising ventricular system. High-resolution thorax CT with lung parenchyma window.* **D:** *coronal reconstruction. Axial section showing an increase in pulmonary attenuation associated with left basal consolidation and air bronchogram (arrow).* **E-F:** *tarnished glass areas with a cottony appearance (e,f, arrow).*

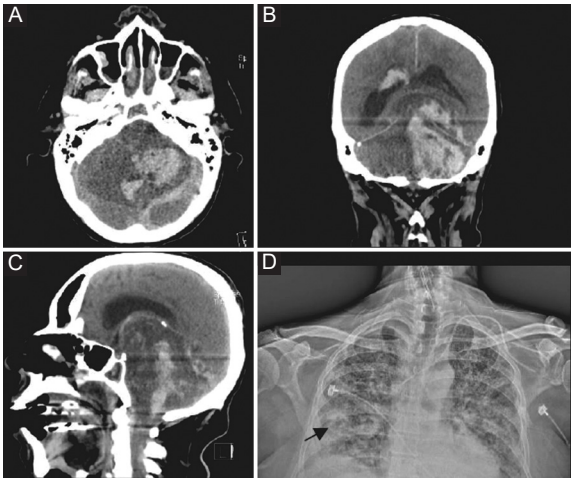

Figure 2. A-D: *brain CT and chest X-ray of patient 2.* **A-D:** *axial reconstruction of simple brain CT.* **A:** *large left cerebellar hemorrhage.* **B:** *coronal reconstruction brain CT, extension of the cerebellar hemorrhage through the left occipital lobe and presence of ventricular disruption.* **C:** *infarction of the brainstem and hemorrhage within the fourth ventricle.* **D:** *AP chest radiograph showing multiple bilateral alveolar-type infiltrates, some of which are nodular in appearance.*

assessment was made in de ICU 8 days posterior to admission, finding the patient with clinical data of brain death, could not performed EEG, so we concluded that the patient was not a candidate for surgical treatment due to clinical conditions and poor prognosis. On his 9th day of hospitalization, the patient developed multiple organ failure and died (Fig. 2).

Case 3

A 56-year-old male with history of hypertension and long standing DM2 presented with 1 month of asthenia, adynamic, as well as polyuria, malaise and, intermittently non-productive cough. He presented with 1 month of asthenia, adynamic, as well as polyuria and malaise, also intermittently non-productive cough. He arrived at ER of our hospital, presenting 12 h before admission with severe headache and pain in the left arm with subsequent monoparesis, and posterior progression to the ipsilateral pelvic limb. He attended with a chest and brain CT, where it was documented right thalamic hemorrhage with extension to the ipsilateral basal ganglia, supratentorial ventricular disruption, without signs of hydrocephalus. Chest CT showed images of ground-glass panlobar affection of bilateral distribution, with a tendency to the right basal consolidation, compatible with SARS-CoV-2 pneumonia. At

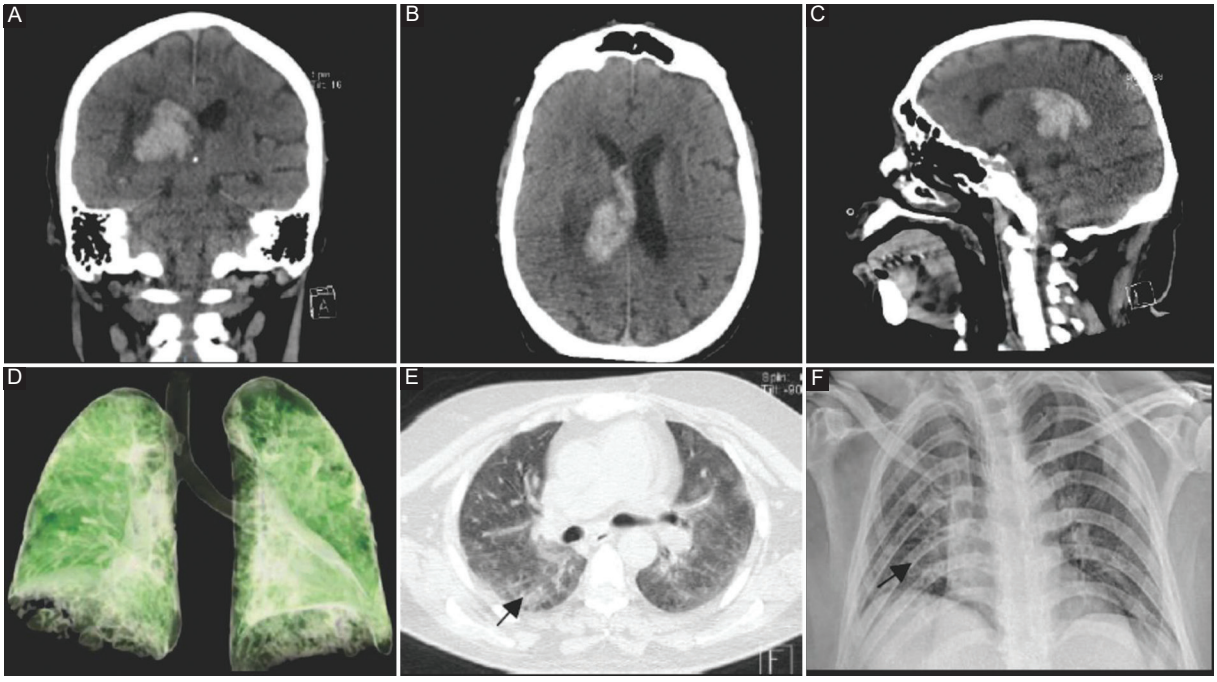

Figure 3. A-F: *CT and X-ray examinations of brain and chest of patient 3.* **A-C:** *multiplanar reconstruction of brain CT showing right thalamic hemorrhage and presence of ventricular disruption. D: 3D reconstruction of pulmonary parenchyma showing bilateral alveolar infiltrates.* **E:** *High-resolution chest CT with lung parenchymal window, axial section showing a slight increase in density, corresponding to a frosty glass pattern, predominantly basal and peripheral bilaterally.* **F:** *chest radiograph showing bilateral ground frosted glass pattern areas predominantly in both lung bases.*

the moment of the patient's evaluation, he was found with 14-point Glasgow Coma Scale (GCS), left hemiparesis associated to hemi-hypoesthesia, hyperalgesia, and ipsilateral allodynia. Neurosurgical treatment was ruled out at that time. He was admitted to pneumology area due to PCR confirmatory test for COVID-19. He was kept on follow-up by neurosurgery. He evolved torpidly with renal failure, increased ferritin (556 ng/ml) and LDH ↑ (293 U/L), without elevations of other acute-phase reactants. A new brain CT scan was performed, in which bleeding reabsorption was observed, with no increase of ventricular size. He continued to manage in the pneumology hospitalization area, ICU management was not required. Ten days after admission, he began with coagulation disorders characterized by thrombocytopenia (114,000) and elevation of fibrinogen (512 mg/dL). D-dimer was not performed. Suddenly began with ventilation distress, presenting cardiorespiratory arrest, basic and advanced measures of resuscitation were started, without recovery (Fig. 3).

Case 4

A previously healthy 84-year-old woman is referred to the ER for presenting sudden weakness of upper and lower right limb, followed by a fall from her plane of support, 3 days before her hospital admission. Subsequently, presented mild dysarthria and drowsiness, loss of consciousness was denied. During her neurological examination, clinically with 13-point GCS, language disturbance and, mild monoparesis of the right thoracic limb. Initial blood tests were unaltered. Simple brain CT scan was performed, in which left thalamic hemorrhage with extension to the basal ganglia was observed, without ventricular disruption or hydrocephalus. It was also found ground-glass pattern with a tendency to consolidation, predominantly on the right side, as well as atelectasis of bilateral basal location, compatible with SARS-CoV-2 infection in the chest CT. Neurosurgical treatment was ruled out at that time. She was admitted to the infectiology area where she remained under surveillance and only symptomatic management. A COVID-19 test was performed by PCR, with a positive result. During her stay, a significant increase in D-dimer (4476 ug/L), fibrinogen (413 mg/dL), and mild thrombocytopenia (110,000 platelets) was observed. A new brain tomography was performed, only bleeding reabsorption was observed. After 5 days of following up, she presented favorably conditions, so she was hospital discharged (Fig. 4).

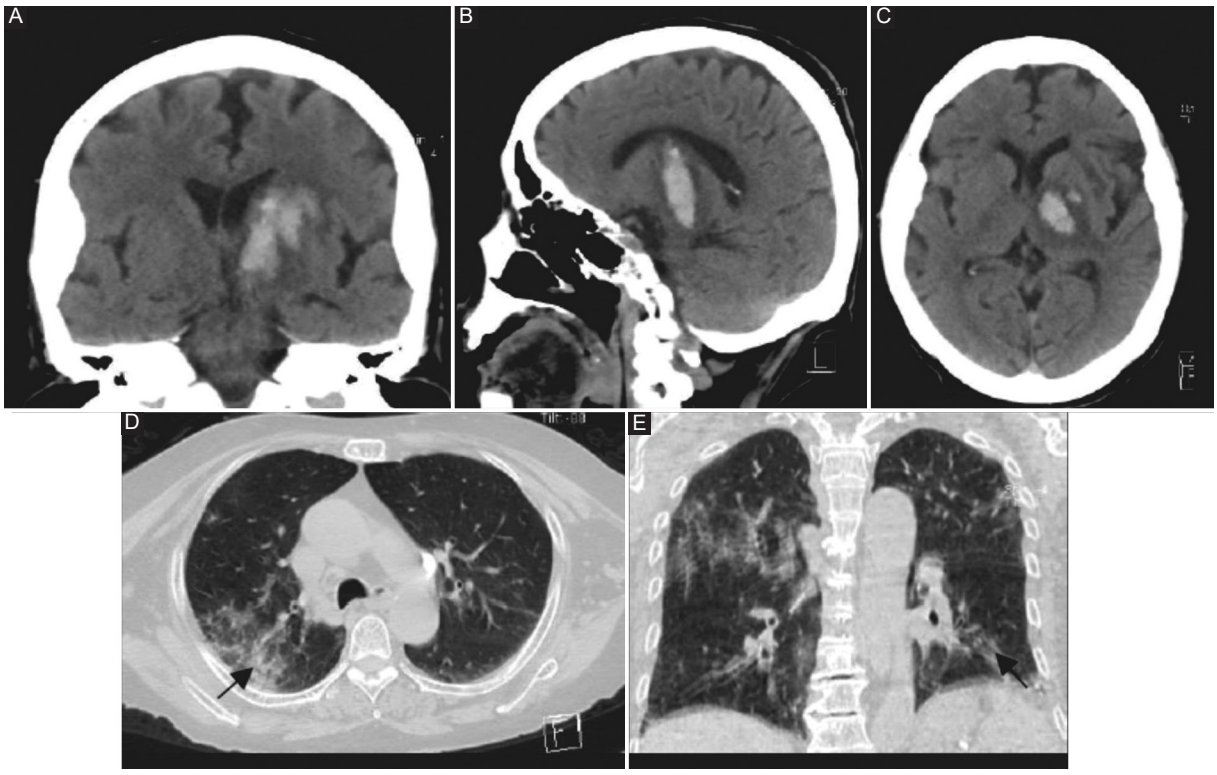

Figure 4. A-E: *chest and brain CT examination of patient 4 a-e.* **A-C:** *presence of a left thalamic hemorrhage with extension to ipsilateral basal ganglia, no ventricular disruption.* **D:** *axial reconstruction with high-resolution chest CT lung parenchymal window showing the greatest damage in the posterior segment on the right side.* **E:** *coronal reconstruction shows presence of areas with a slight increase in density, corresponding to a ground-glass pattern with a tendency to consolidate. Atelectasis of posterior location and bilateral baseline is observed.*

Discussion

The neurological manifestations of COVID-19 infection are frequently documented, and this has been explained by the neurotropism of the virus. In our series, two patients debuted with HS as part of the initial symptoms of COVID-19, while two were in the context of critically ill patients and as a late complication of the disease. Various routes of invasion to the CNS have been proposed, the main ones: (1) by direct ascent through the cribriform plate from the nasal mucosae, (2) by retrograde axonal transport trough the olfactory nerve, and (3) by the hematogenous route, directly infecting endothelial cells of the brain–blood barrier (BBB), epithelial cells of the BBB of the choroid plexus or using peripheral inflammatory cells that cross the BBB to invade the CNS[8,10,11].

It is necessary to recognize in the first instance that, given the high proportion of patients with SARS-CoV-2 infection, and the high prevalence of cardiovascular risk factors in the Mexican population, the occurrence of HS may be more a coincidence than a causality[12].

The previous studies demonstrated thrombocytopenia in 4% of non-severe cases of COVID-19[13], but up to 57.7% of severe patients have < 150,000 and 8% < 100,000 platelets[3,13]. Interestingly, in patients with any neurological symptoms, platelet levels are significantly lower than patients without neurological symptoms[4]. Thrombocytopenia was found among our patients in two cases. This fact associated to the enoxaparin use in two of our patients, could increase the risk of HS.

Retrospective studies of patients with COVID-19 have found high prevalence of hypertension, DM2, and smoking (major risk factors for HS), especially in critically ill patients[3-5,13]. Regarding hypertension, the reported prevalence for non-critical patients is 14%, compared to 15-23.7% in critical patients[3,13], and the proportion is surprisingly higher in those critical patients who had some neurological manifestation 36.4-66%[4,5]. This could be due to a deregulation of the blood pressure control system. For its entry into cells, SARS-CoV-2 uses glycoprotein S to bind to the receptor for angiotensin-converting enzyme 2 (ACE2), which is expressed in the lungs, arteries, heart, kidneys, endothelial BBB cells, and glial cells[8,14,15].

Furthermore, it has been shown that patients with DM2 and prior smoking have higher ACE2 receptor expression, a finding attributed to a chronic ischemic condition[7]. Negative regulation of the expression of ACE2 can affect the endothelial function of the cerebral vessels, increase the local concentration of angiotensin II, and raise blood pressure, for this reason, patients with COVID-19 have a higher risk of developing HS because of uncontrolled previous underlying hypertension[7,9,15].

Another important effect of the downregulation of ACE2 is the loss of vascular (vasodilation) and anti-inflammatory (antifibrotic) protective effects, causing endothelial damage, which converges in the sequence of another pathophysiological mechanism of SARS-CoV-2: uncontrolled immune response. This immune cascade causes a pro-inflammatory state mediated by IL-6 and IL-8, leading to a cytokine storm responsible[7,9,16,17]. In this study, three of our cases had significant elevation of acute-phase reactants (C-reactive protein, ferritin, and D-dimer). It has recently been postulated that HS is actually a systemic disease with an important role for the immune response in pathogenesis and prognosis[18]. D-dimer that reflects the activity of the coagulation and fibrinolytic systems has been previously described as a major risk factor for intracranial hemorrhage and death[19,20]. Elevated ferritin has been associated with severity and poor functional outcome in HS patients, presumably by overregulating secondary brain damage increasing perihematomal edema[20,21]. Furthermore, C-reactive protein is an useful prognostic predictor for HS patients[20,22,23]. The poor prognosis of HS associated to COVID-19, in three of our cases, can be explained in the first place by the severity of the pneumonia, the association to HS, and the inflammatory overresponse that confers endothelial damage and multiorgan failure.

In the literature review and this case series lead the authors to some reflections: although the immune response induced by the virus or the virus itself is unlikely to cause structural damage to a vessel and lead to HS[16], it is feasible to assume that other mechanisms already described, such as uncontrolled blood pressure, coagulopathy, thrombocytopenia, and immune response could synergize so that a patient at prior risk is triggered by SARS-CoV-2 to HS[11]. This idea is indirectly supported by the GHM cases, given that they are patients with high risk for HS, with a median age of 70.5 years, cardiovascular risk factors, classic sites of hypertensive cerebral hemorrhages (two thalamus and two dentate nucleus), and with a huge immune response manifested by biochemical alterations. In contrast with patients with ictus in Wuhan with age around 30s and de US patients with median age of 50 s[4,6].

Likewise, for patients requesting medical attention in the ER with any neurological symptom, including HS, ER team should consider the possibility of infection by SARS-CoV-2, requesting within their study protocol a chest CT and a COVID-19 test. Unfortunately, at the moment, we have not fully understood the pathophysiology of SARS-CoV-2 infection. As new studies are conducted, we will be able to elucidate this clinical entity.

Conclusions

To the best of our knowledge, these four cases represent the largest series of patients reported with HS during the current COVID-19 pandemic in Mexico. Unfortunately, we observed high mortality by the combination of pneumonia, HS, and comorbidities. HS should be considered as differential diagnosis in cases of neurological impairment in a previous stable patient and should prepare neurosurgery teams for the timely and appropriate treatment of HS COVID-19 patients.

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Conflicts of interest

There is not any affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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