



Encephalitis associated with Covid-19 and thunderclap headache: an unusual relationship

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Abstract

The Covid-19 is characterized mainly by respiratory symptoms, however this virus frequently damages the nervous system, although the exact mechanism involved is still unclear. Headache is the most common neurological symptom and has a great heterogeneity, including thunderclap headache which should be considered a red flag on emergency departments.

Objectives

The case of a 51 years-old woman with thunderclap headache started seven days before, which progressed with mental confusion, inattention and language plus memory disturbance on the day of admission, is reported. General physical examination was normal except for the presence of borderline pyrexia (37.7 °C). Neurological examination showed no particularities, except for mental and cognitive alterations. Computed angiography of the brain excluded bleeding but showed one aneurysm. Cerebrospinal fluid (CSF) had no xanthochromia, but evidenced a lymphomonocytic pleocytosis with discrete hyperproteinorraquia. Due to hospital protocol the patient underwent computed tomography of thorax and we found ground-glass opacities suggesting viral infection. Then, RT-PCR for Sars-CoV-2 with nasopharyngeal swab and in CSF was performed with both positives. Therefore, the diagnosis was encephalitis associated with Covid-19. We opted for supportive care only. Patient evolved with many complications, need of ventilatory support and renal replacement therapy, but she was discharged after 35 days with no symptoms and at follow-up, two months later, the only finding was mild inattention.

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Introduction

The disease caused by the novel coronavirus is classically characterized by the involvement of the respiratory system however it has a wide spectrum of manifestations, including damage to the nervous system (NS). Retrospective study developed in Wuhan in 2019 with 214 patients, still at the beginning of the pandemic, showed a prevalence of neurologic manifestations of 37%.¹ The most common neurological symptom reported was headache, with different characteristics and great heterogeneity among those affected.²

Thunderclap headache, as the name says, is a sudden severe pain usually caused by potentially serious disorders, mainly vascular disturbances, therefore it consists of a medical emergency, especially when associated with altered mental state.³ In a recent study with 262 patients with Covid-19 and headache around 25% presented severe or very severe pain.² Another publication with 2,194 participants evidenced that red flags for headache were present in 61% of the cases, but confusion was the warning sign only in 6.2% and sudden onset just in 5.8%.⁴

Here we report a case of a patient admitted at a hospital reference in neurology with a suspect of hemorrhagic stroke with a history of thunderclap headache plus altered mental state without systemic symptoms and after investigation, surprisingly, diagnosed with encephalitis associated with Sars-CoV-2.

Case Report

Woman, 51 years-old, previous history positive just for depression and systemic arterial hypertension, non-smoker. Admitted at hospital reference to neurology with suspicion of hemorrhagic stroke, reporting seven days of holocranial and sudden headache that has progressed to severe intensity within minutes at onset. Associated with evolution to mental confusion, inattention, inability to meet family members and difficulty of communicating at the day of admission.

Admitted normotensive (130/70 mmHg), normocardic (96 bpm), saturating 97% without oxygen supplementation, without respiratory distress and with a borderline pyrexia of 37.7°C. General physical examination, including respiratory auscultation, was normal. In the neurological examination of admission, the patient was inattentive, hypocontactant, drowsy but awake with verbal stimulus, disoriented in time and space, unable to say her own

name or recognize her husband and with a language disturbance, characterized by relative fluent speech, incapacity to name objects, repeat words or phrases and to obey commands. The muscular tonus was normal and the patient moved the four members without fall in deficit maneuvers. She had no signals of pyramidal liberation or any other alteration at neurological examination, including absence of neck stiffness.

General laboratory tests were normal. Brain and neck computed angiotomography (CTA) excluded acute bleeding, however showed one saccular aneurysm with 1.2 x 0.9 millimeters in the supraclinoid/paraophthalmic segment of the left internal carotid artery (Figure 1).

We performed cerebrospinal fluid (CSF) mainly with the objective to rule out subarachnoid hemorrhage (SAH) and the liquid was clear without xanthochromia, but with slight lymphomonocytic pleocytosis (8 leukocytes), discrete protein elevation (53 mg/dL) and 34 red blood cells. Electroencephalogram (EEG) showed symmetrical and disorganized brain electrical activity with poor anteroposterior differentiation, theta rhythm diffuse and presence of triphasic waves, suggestive of an encephalopathy.

Due to the hospital protocol during the Covid-19 pandemic, the patient underwent computed tomography of the thorax and we found ground-glass opacities involving around 25% to 50% of the lungs, predominantly at peripheral regions, suggesting viral infection (Figure 2). Therefore, RT-PCR for Sars-CoV-2 with nasopharyngeal swab was performed with a positive result. Family members denied respiratory complaints or any other symptoms and denied contacts prior to the admission with confirmed or suspected cases of coronavirus disease. The patient had not traveled recently. The patient did not perform magnetic resonance imaging due to the institution's isolation rules for cases of coronavirus disease.

After that, added to the exclusion of hemorrhagic stroke and SAH, our suspicion was viral encephalitis. We started empirical treatment with acyclovir and solicited serologies at cerebrospinal fluid for herpes simplex virus and for Sars-CoV-2. The first result was negative, so the acyclovir was suspended and the last result was positive, confirming the diagnosis of Covid-19 encephalitis.

We opted to maintain just supportive care, without immunosuppressive treatments. During hospitalization, the

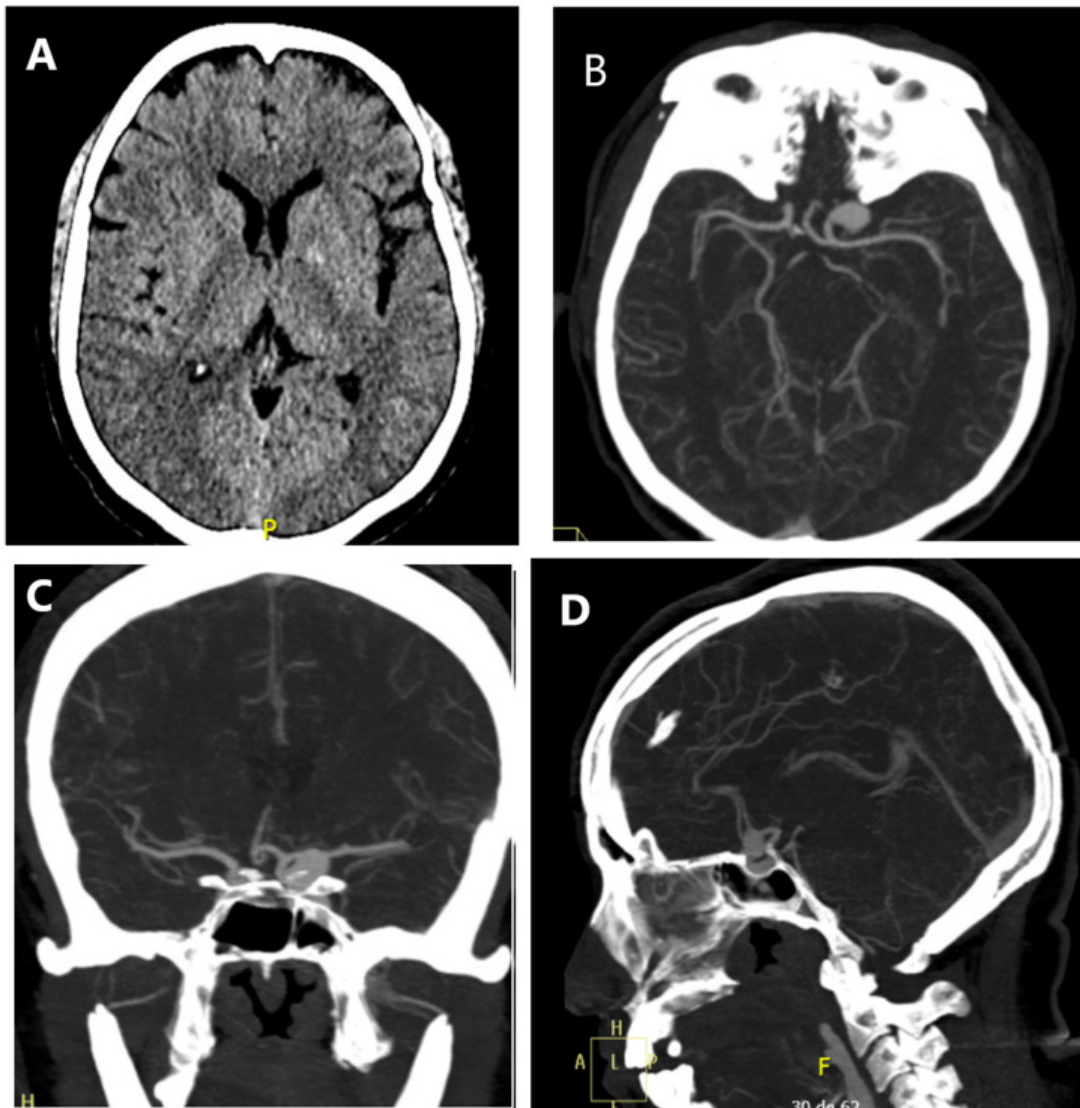


Figure 1. A: Head computed angiography - precontrast phase without acute bleeding; B: Head angiography - axial section evidencing a saccular aneurysm with 1.2 x 0.9 millimeters in the supraclinoid/paraophthalmic segment of the left internal carotid artery; C: Head angiography - coronal section evidencing the aneurysm described above; D: Head angiography - sagittal section evidencing the aneurysm described above.

neurosurgery team evaluated her because of the aneurysm visualized on CTA and they opted for conservative treatment. The level of consciousness of the patient worsened progressively and she developed an aspiration pneumonia, requiring orotracheal intubation. At the intensive care unit (ICU), even under the influence of sedatives, the patient presented diffuse myoclonus, pyramidal signs and spasticity diffuse, suggesting seizure and managed with phenytoin and dose adjustment of sedatives. A new EEG evidenced occasional epileptiform disorders in the left temporal region with one electrographic seizure, but without alterations compatible with status epilepticus.

For 30 days, she remained at ICU, requiring multiple cycles

of broad-spectrum antibiotics and renal replacement therapy, progressing to the need for tracheostomy with subsequent decannulation. She was discharged from hospital 35 days after admission, alert, with no language or memory disturbance, oriented in time and space. On follow-up, two months later, the patient presented just mild inattention, without impact on their usual activities.

Comments

Headache is a common complaint in emergency departments/hospitals and one of the scariest etiologies is SAH, with rates of mortality of up to 65% and misdiagnosis of up to 51%.⁵ Almost 70% of these cases

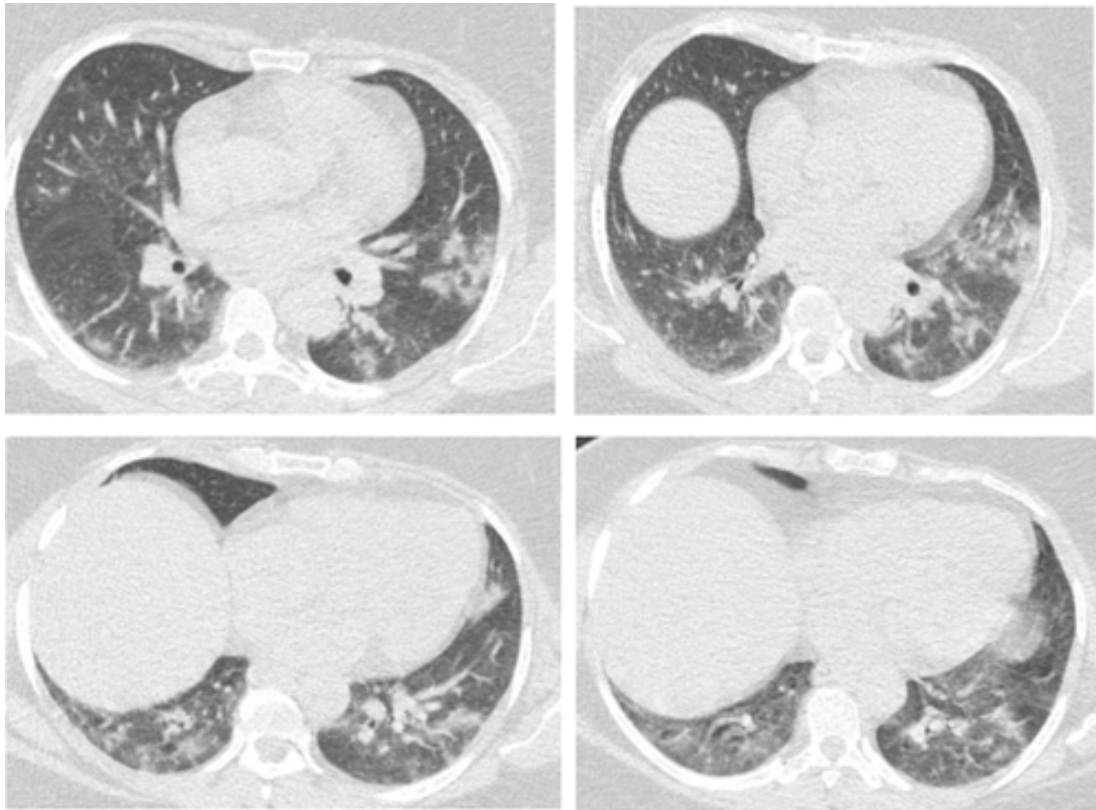


Figure 2. Computed tomography of thorax evidencing ground-glass opacities and sparse bilateral foci of consolidation, predominantly in the peripheral with pulmonary involvement around 25-50%.

will present headache as the first symptom and, although not well described in literature, around 50% of the patients will experience the thunderclap headache.⁵ Considering all of the above, faced with a case as we describe here, with thunderclap headache and neurological findings, investigating SAH is mandatory.

The first step in the investigation is the head computed tomography (CT).⁵ Usually CTA is performed after confirmed SAH for screening of aneurysms (the most common cause of SAH) and/or program the therapeutic or when the diagnosis is still a doubt.^{5,6}

In our case, we performed the CTA first because in our institution this exam can be realized as fast as the CT without delaying the diagnosis and has a high sensitivity to detect aneurysms.⁶ This exam in our patient did not detect bleeding, but identified one aneurysm. After three days of the symptoms onset the sensitivity of CT starts to decrease and almost half is negative for SAH after seven days, often necessitating a lumbar puncture (LP) and the presence of xanthochromia in the CSF is suggestive of SAH because of heme metabolism.^{5,6} Considering the symptoms reported on admission, the time of evolution and the detection of

aneurysm on CTA we proceeded to the next step and performed a LP that did not show xanthochromia. CSH is also useful for differential diagnostics and in our case was the key point.

According to the literature, infection can be the cause behind a thunderclap headache.³ The pathophysiological mechanism involved in the neurological manifestations of SARS-CoV-2 is still unclear, but invasion of the NS can occur by transsynaptic transport or by hematogenous dissemination, in addition, this virus can lead to an exacerbated immune response that damages NS.⁷

Recent review with 2,194 cases of Covid-19 identified a prevalence of headache of 30%, however just around 6% had this as the first symptom and more than 90% had systemic symptoms.⁴ Red flags around headache were present in 264 participants but as we described at the introduction, altered mental state and sudden onset occurred in a few cases.⁴ Contrasting with that here we present a case characterized by intense and sudden headache that evolved for altered mental state without systemic symptoms and without any suggestion of respiratory infection, except by the presence of borderline pyrexia.



Encephalitis associated with Sars-CoV-2 is a rare neurological manifestation and altered level of consciousness and/or mental state, seizures, headache and weakness are the most frequent presentations.^{7,9} In accordance with the literature, our patient had almost all these symptoms. The detection of the virus at the CSF is very uncommon^{7,8}, in contrast to that the RT-PCR for Sars-CoV-2 of our patient was positive.

Patients with Covid-19 and encephalitis have a poor prognosis compared to others affected by such virus⁹ and, unfortunately, until now we do not have a standardized treatment.^{8,9} Here we report a case that presented serious complications, but had an excellent recovery, even without immunosuppressive treatments.

In conclusion, the authors want to point out that headache is a common symptom in the emergency departments in patients with Covid-19 or not. It can be the first signal of the novel coronavirus infection or of a complication of that, like encephalitis. In addition, the pain has a very range of phenotypes including thunderclap headache mimicking an SAH, as we approach here. Therefore, in the context of a contagious pandemic disease health professionals have to be prepared for the prompt recognition of this infection.

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