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CASE REPORT

Cerebral microbleeds in a COVID-19 patient

B. Maatman[1], E. Aronica[2], S.D. Roosendaal[3], D.C. Velseboer[1]

Departments of [1]Intensive care , [2]Pathology and [3]Radiology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

Correspondence

B. Maatman - b.maatman@amsterdamumc.nl

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Abstract

A 31-year-old male was admitted to the intensive care unit with respiratory failure due to SARS-CoV-2 infection. A persistent altered mental state, with agitation and subsequently persistent coma, was one of the complications he suffered during his illness. Brain MRI showed diffuse cerebral microbleeds (CMBs). The pattern of distribution resembled the CMBs that have been described earlier in critically ill patients. Post-mortem analysis of brain samples confirmed CMBs and additionally showed diffuse subcortical hypoxic white matter damage. We suggest that cerebral hypoxia may cause CMBs in COVID-19 patients in a similar way to other well-described causes of hypoxia. Furthermore, we want to bring to attention that coma in COVID-19 patients with CMBs may be associated with diffuse subcortical white matter injury not visible on brain MRI.

Introduction

COVID-19 is a novel viral disease in which knowledge regarding disease epidemiology and clinical presentation has been rapidly evolving in the past months since the initial identification. In addition to respiratory failure, severe neurological sequelae associated with COVID-19 have been described, including encephalitis, acute necrotising encephalopathy and cerebrovascular disease.[1,2] In this case report we present a distinct neurological complication in a COVID-19 patient, possibly associated with hypoxic episodes.

Case report

A 31-year-old male with a history of substance abuse was admitted to the emergency room of a general hospital with complaints of dyspnoea, cough and fever of one week duration. The polymerase chain reaction tests on throat and nasal swabs for SARS-CoV-2 upon admission were positive. Chest X-ray revealed bilateral consolidations. Treatment was initiated with ceftriaxone and azithromycin. Four days after admission his respiratory symptoms worsened and he was transferred to the intensive care unit where invasive mechanical ventilation was initiated. At day 31, there was no sign of respiratory improvement and he was transferred to our referral hospital for expertise. During his stay in our department, deep venous thrombosis and pulmonary embolisms were diagnosed for which unfractionated heparin was initiated. He developed bilateral pneumothoraces and chest tubes were inserted. He had persistent fever and positive blood cultures with *Staphylococcus epidermidis* for which vancomycin was administered. Disseminated intravascular coagulation (DIC) was suspected due to widespread petechiae, yet formal DIC calculations were repeatedly inconclusive. Laboratory variables included a nadir platelet count of 103 x 10^9/l, a nadir fibrinogen level of 3.5 g/l, a peak D-dimer of 3.47 mg/l and a peak INR of 1.3. Despite proning, high PEEP level and intermittent neuromuscular blocking agents, he had recurrent episodes of severe hypoxaemia lasting for hours. During his stay, his altered mental state was a major concern, fluctuating between agitation and coma. Discontinuation of sedation for agitation initially improved his consciousness. However, at day 36 he relapsed into a coma (Glasgow Coma Score: E1M1Vnt (not testable in an intubated patient)) and after this there were no signs of neurological recovery. There were no abnormalities on repeated CT scans of the brain. An EEG showed diffuse slowing consistent with encephalopathy and no signs of epilepsy. A lumbar puncture was performed and analysis of cerebrospinal fluid showed no abnormalities. MRI of the brain demonstrated diffuse cerebral microbleeds (CMBs), with a high density in the corpus callosum and subcortical white matter, consistent with the pattern of distribution of critical illness-associated CMBs (*figure 1*).[3] Forty-six days after admission there was still no improvement in his neurological and respiratory condition, and his treatment was discontinued. Analysis of autopsy samples of the brain showed multiple CMBs with a dense concentration in the frontoparietal subcortical region and corpus callosum (*figure 2*). In addition, diffuse subcortical hypoxic white matter injury, an increased microglial activity with disruption of the blood-brain barrier and micro infarctions with micro calcifications were seen (not shown in figure).

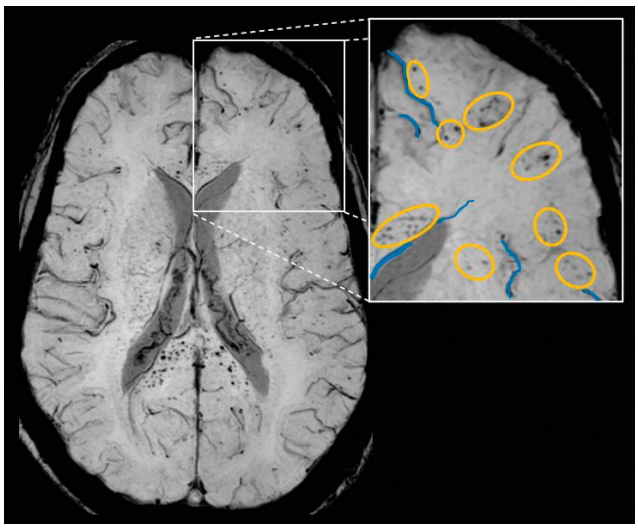

Figure 1. Axial susceptibility-weighted image (SWI) shows numerous punctiform susceptibility artifacts in the brain (in neuroradiological reports termed 'microbleeds'). They are located mainly in the corpus callosum (genu and splenium are visible here) and subcortical white matter. In the close-up of the left frontal area, the 'microbleeds' are encircled; for clarity, veins have been highlighted in blue.

Discussion

Recently, a distinct microbleed phenomenon has been described in the context of critical illness.[3] These CMBs involve the juxtacortical white matter and corpus callosum and spare the deep and periventricular white matter and the grey matter. There is a resemblance with the CMBs that are seen in patients with disease associated with hypo-oxygenation such as ARDS and high-altitude exposure. This suggests that there might be a common pathogenesis were hypoxia plays a significant role.[4,5] Hypoxia-induced hydrostatic or chemical effects on the blood-brain barrier could potentially account for extravasation of erythrocytes.[6] In our patient, oxygenation was compromised due to COVID-19 associated ARDS and recurrent pneumothoraces. The distribution pattern was consistent with the CMBs seen in critical illness and hypoxia-related disease, suggesting that cerebral hypoxia played a role. Although there are emerging data that severe COVID-19 can be complicated by significant coagulopathy, the evidence that therapeutic anticoagulation is effective in these patients remains scarce.[7] Next to this, antithrombotic therapy, initiated after the occurrence of thrombotic complications, may have contributed to the expansion of CMBs. Another possible explanation for critical illness-associated cerebral microbleeds is DIC.[8] Our patient suffered from persistent fever and had petechiae. However, accurate diagnosis of DIC is challenging and in our case formal DIC score calculations were repeatedly inconclusive, despite evidence of increased fibrinogen degradation products and reduced platelet levels. In COVID-19 patients there are other possible explanations for the development of CMBs. A significant consumption coagulopathy can lead to thrombosis in small medullary veins leading to CMBs.[9] It is also worth noting that the spike protein of the SARS-CoV-2 virus has a strong affinity for the angiotensin-converting enzyme 2 (ACE-2) receptor which has widespread expression in endothelial cells.[10] Microscopic disruption of the endothelium in brain tissue may also be responsible for CMBs.[9] In a recent study in COVID-19 patients, with analysis of brain MRIs but no histological examination, CMBs were associated with critical illness, increased mortality, and worse functional outcome.[11]

Spontaneous intracerebral haemorrhage usually results in a focal neurological deficit and is easily diagnosed by CT scan. It is caused by arterial rupture, leads to haematoma formation in the lobar hemispheres or deep grey structures and is associated with high mortality.[12] CMBs, best visualised by MRI, result from disruption of the integrity of the blood-brain-barrier with subsequent erythrocyte extravasation and are usually clinically asymptomatic.[13] CMBs are recognised consequences of cerebral amyloid angiopathy and chronic hypertension and they have been associated with older age, hypertension, smoking, white matter disease, lacunar infarcts, previous ischaemic stroke or intracerebral haemorrhage.[14] Post-mortem studies have shown that CMBs detected on MRI result from the accumulation of blood in the vicinity of pathologically altered vessels.[15] They are associated with surrounding tissue damage, so concomitant brain dysfunction might be possible.[16] Although CMBs are only small in size, in the order of several millimetres, it is not

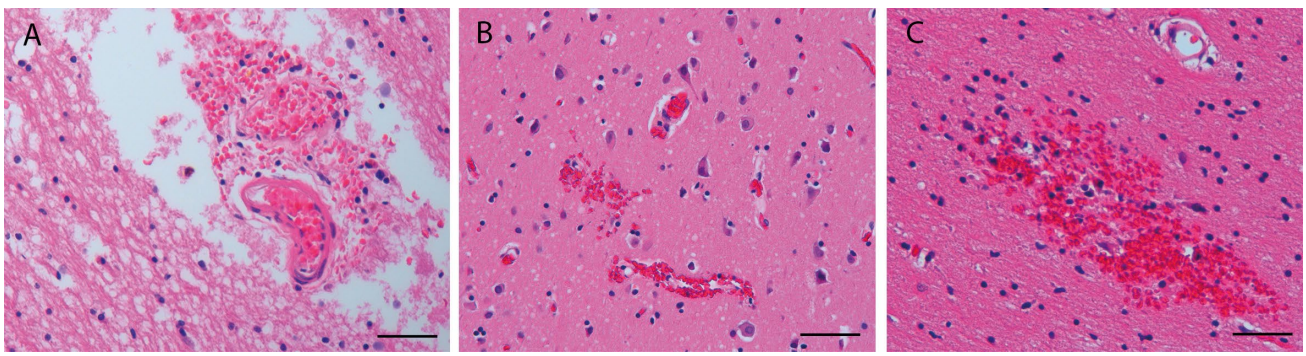

Figure 2. Histopathological specimens of the corpus callosum (A); frontal cortex (B); grey matter (C); stained with haematoxylin & eosin showing extravasation of red blood cells. There was no indication of vasculitis. Scale bars: A, C: 60 µM. B: 100 µM

unreasonable to think that they could cause symptoms if they form rapidly or in functionally strategic locations.[17] Another possibility is that, rather than disrupting function by the direct destruction of tissue, CMBs could disrupt the activity of the surrounding neurons, thus affecting local brain function or connectivity.[18] Moreover, most CMBs contain haemosiderin, a compound that may affect the electrical activity of the cortex and thereby possibly initiate focal seizures.[19] What is more likely than such local effects, is that the accumulation of multiple CMBs over time could have a more insidious effect on the brain functions that depend on the integrity of widespread anatomical networks, for example cognition or gait.[20] Although these are plausible mechanisms by which CMBs could cause clinical symptoms, the evidence that CMBs independently affect brain function or cause focal neurological symptoms through associated tissue damage remains limited.[21]

The consciousness of our patient was fluctuating between agitation and coma, and was initially clouded by sedatives to decrease his agitation. An EEG showed diffuse slowing consistent with encephalopathy, which has been described in another COVID-19 patient with CMBs and coma.[22] Finally, persistent coma was the reason to perform an MRI of the brain, which revealed the presence of CMBs. The contribution of these CMBs to his coma is difficult to determine. The involvement of strategic locations, such as the basal ganglia, and extensive number of CMBs suggests that it played a role in the development of coma. More likely, the coexistent histological presence of diffuse subcortical white matter hypoxic injury and micro infarctions played a more significant role in the development of coma. This combination of CMBs and subcortical white matter injury, without typical features of viral or post-viral encephalitis, has recently been described in the context of COVID-19-associated neuropathology.[11, 23]

A challenge for future research is studying how CMBs could affect the brain since they are closely linked to many manifestations of cerebrovascular disease. Moreover, in COVID-19 the independent contribution of CMBs to disability and death is uncertain. Fundamental research is needed to unravel the association between SARS-CoV-2 infection and cerebral CMBs, and provide answers whether the CMBs develop secondary to hypoxia or to other COVID-19-associated factors.

Conclusion

In this case report we present a patient with a fatal SARS-CoV-2 infection with severe neurological complications. The pattern of distribution of CMBs was similar to other disease associated with hypoxaemia. We suggest that the recurrent and prolonged hypoxic episodes may have played a role in the development of critical illness-associated CMBs. Furthermore, we show that SARS-CoV-2 infected patients with CMBs may also have diffuse subcortical hypoxic white matter lesions on post-mortem analyses, not detected by MRI. We recognise the limitations of this single case report and acknowledge that additional studies are necessary to establish a connection between hypoxaemia, CMBs and coma in COVID-19 patients.

Disclosures

Written informed consent was obtained from the patient's family for the publication of this case report. All authors declare no conflict of interest. No funding or financial support was received.

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