

COVID-19-related vasculopathy of the brain

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SUMMARY

The COVID-19 pandemic is revealing growing reports of atypical presentation of the disease beyond the respiratory system. SARS-CoV-2 infection has been linked to multisystem vasculopathy including cardiopulmonary, cerebral and renal vasculature, potentially brought on by a dysregulated host immune response in a probable setting of a cytokine storm. Here, we describe a case of a previously healthy and active 74-year-old man presenting with acute cognitive decline with preceding non-specific influenza-like symptoms. He was then diagnosed with cerebral amyloid angiopathy (CAA)-associated intracerebral haemorrhage and was found to be COVID-19 positive. COVID-19-induced immune response may have further compromised the cerebral vessels already weakened by CAA, triggering multiple microhaemorrhages leading to clinical presentation. The limited evidence about the heterogeneity of COVID-19 manifestations suggests that clinicians should be aware and screen for concurrent COVID-19 in patients presenting with neurological features during the peak of this pandemic, as this offers the best chance for better clinical outcome.

BACKGROUND

COVID-19 has been declared a pandemic by the WHO on 11 March 2020. As of today, a large part of the world is still struggling to contain this highly contagious disease. The clinical presentation of COVID-19 infection is diverse and may include cough, myalgia, headache, diarrhoea and smell or taste disorders.¹ Pulmonary complications are the most frequent serious manifestations of the infection. Although our understanding of this disease has progressed at an incredible speed, there remains much to be learnt. There is increasing literature regarding neurological manifestations in COVID-19 infection including cerebrovascular accidents.²⁻⁷ Intracerebral bleeds in COVID-19 remain a rare occurrence. It is currently still unclear to what extent COVID-19 contributes towards the pathophysiology of haemorrhagic stroke.

CASE PRESENTATION

A 74-year-old man presented to the hospital in an acute delirious state. Detailed history was obtained from his wife whom he lived with. There was a 3-week history of fever, rigours, altered taste sensation, lethargy, headache and diarrhoea. He had also lost one stone of weight during this period. There were no respiratory symptoms. On the day of admission, his wife reported an acute change in his behaviour and confusion. He has a background of well-controlled hypertension on single antihypertensive (lisinopril 20 mg once

a day) and glaucoma. Before the onset of these symptoms, he was a very active man who went for daily walks and enjoyed hiking once a week for an average of 8 miles. He was not known to have any significant family history.

On arrival to the accident and emergency department, physical examination revealed a lean man who was alert but confused, with a Glasgow Coma Scale (GCS) of 13 (E4 V4 M5). There was no focal neurology. Vital signs were within normal limits (table 1). Initial infection screen was unremarkable: Blood tests showed mild lymphopenia $1.0 \times 10^9/L$ and mild neutrophilia $8.8 \times 10^9/L$; platelets and C reactive protein (CRP) were within normal limits (table 2); chest X-ray showed no evidence of consolidation; urine culture was negative.

Urgent brain CT scan was performed and showed multiple acute intra-axial haematomas in the left frontal lobe. Subsequent brain MRI and angiography demonstrated cerebral amyloid angiopathy with numerous microhaemorrhages and small intraparenchymal bleeds (figure 1).

INVESTIGATIONS

Various diagnostic tests were carried out to exclude a reversible cause of the CAA, which include infection and autoimmune causes.

The first lumbar puncture carried out revealed a cerebrospinal fluid (CSF) with raised red cell count and white cell count that was predominantly lymphocytic and raised protein and normal glucose as shown in table 2. Gram stain and culture for bacterial growth, virology and fungal screen were negative. Due to the very high CSF protein, a tuberculosis screen on both CSF and peripheral blood was performed, and these were negative. Workup for autoimmune causes of encephalitis was also sent including anti-glutamic acid decarboxylase, N-methyl-D-aspartate, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, leucine-rich glioma activated 1, contactin-associated protein 2, thyroid peroxidase and collapsing response mediator protein antibodies; all of which were negative. In addition, CSF cytology screen was requested to exclude malignant meningitis, and this was also negative.

On day 5, there was no change in the patient's clinical state except for some episodes of mild fever. Repeat blood tests revealed a consistent lymphopenia (table 2). Unfortunately, there was no result regarding SARS-CoV-2 infection at this point due to a lab error. A second lumbar puncture was carried out to further exclude malignant meningitis or autoimmune causes. CSF results continued to show raised lymphocytes with raised protein and normal glucose (table 2).



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Table 1 Vital signs

Blood pressure (mm Hg)	130/85
Heart rate (beats/minute)	75
Respiratory (breaths/minute)	17
Oxygen saturations	99% on room air
Temperature (degree Celsius)	36.5

On day 10, the patient's SARS-CoV-2 oropharyngeal and nasal swab returned a positive result, and the patient was isolated. A thorax–abdomen–pelvis CT scan, originally obtained to rule out an underlying malignant process, revealed bilateral pulmonary ground-glass opacities indicative of atypical infection. There was no evidence of malignancy.

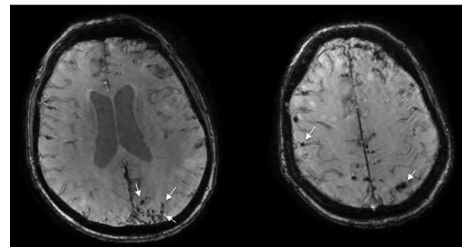


Figure 1 MRI brain identified multiple intracerebral microhaemorrhages and small intraparenchymal bleeds (white arrows pointing to areas of microhaemorrhages).

DIFFERENTIAL DIAGNOSIS

Given that the CSF had very high protein with raised lymphocytes, extensive investigations were carried out to rule out viral, fungal, bacterial, autoimmune and malignant aetiology as mentioned above. An MRI angiogram showed no changes to

Table 2 Laboratory investigations

Investigation	Normal value	Day 0	Day 3	Day 10
Haemoglobin	130–180 g/L	150	156	166
White cell count	4.0–11.0×10 ⁹ /L	10.3	9.8	5.4
Neutrophils	2.0–7.5×10 ⁹ /L	8.8	8.4	4.6
Lymphocytes	1.5–4.0	1.0	0.7	0.6
Platelets	130–400×10 ⁹ /L	224	171	109
Sodium	133–146 mmol/L	134	143	141
Potassium	3.5–5.3 mmol/L	4.3	4.0	3.7
Urea	2.5–6.5 mmol/L	4.9	6.5	5.8
Creatine	54–110 umol/L	84	66	58
Estimated GFR (mL/min)		83.8	>90	>90
C reactive protein	0–8 mg/L	6	6	95
Glutamic acid decarboxylase antibody	Negative			
N-Methyl-D-aspartate antibody	Negative			
α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antibody	Negative			
Leucine-rich glioma activated 1 antibody	Negative			
Contactin-associated protein 2 antibody	Negative			
Thyroid peroxidase antibody	Negative			
Collapsing response mediator protein antibodies	Negative			
<i>Borrelia</i> serology	Negative			
HIV	Negative			
Tuberculosis Quantiferon test	Negative			
Hepatitis B and C viruses	Negative			
<i>Treponema pallidum</i> particle agglutination assay	Negative			
Autoantibody screen*	Negative			
Cerebrospinal fluid normal value		Day 3		Day 10
Glucose level	2.50–4.50 mmol/L	2.96 mmol/L		2.94 mmol/L
Protein level	0.15–0.45 g/L	5.55 g/L		5.36 g/L
Total red cells		3717×10 ⁶ /L		
Total white cells		153×10 ⁶ /L		
Lymphocytes		80%		
Gram stain		No organisms seen		No organisms seen
Culture		No growth		
Cryptococcal antigen		Not detected		
Enterovirus, parechovirus, HSV1, HSV2, VZV DNA		Not detected		
Cytology		No malignant cells		
Serum glucose		6.6		
		Day 10		
SARS-CoV-2 RNA nose and throat swab		Detected		

* Antinuclear antibody, anti-double stranded DNA antibody, anti-extractable nuclear antigen antibody, antimitochondrial antibody, smooth muscle autoantibody, parietal cell antibody, Liver-kidney microsomal antibody.
GFR, Glomerular Filtration Rate; HSV, Herpes Simplex Virus; VZV, Varicella Virus.

suggest vasculitis. There were no changes of inflammation on the MRI brain scan or any asymmetrical subcortical white matter disease on CT to suggest CAA-related inflammation. Furthermore, there was no corresponding oedema on the T2-weighted MRI images when compared with the gradient echo images of the same areas of the brain demonstrating microhaemorrhages (figure 2). This appearance would not be consistent with an inflammatory form of CAA. The extensive workup was negative apart from COVID-19 infection. There was also no sign of spinal cord injury to suggest spinal block as the cause of the raised CSF protein. The ongoing and numerous microhaemorrhages and subsequent damage to the blood–brain barrier were thought to be the cause of the raised CSF protein.

TREATMENT

After consultation with the microbiology team, the patient was initially treated empirically with a course of intravenous acyclovir and meropenem, which did not result in any clinical improvement. In addition, specialist neurology and neurosurgical advice was sought regularly. As CAA is largely an irreversible condition, no other specific pharmacological treatment was instigated. Management strategies were largely conservative. The patient's blood pressure was maintained at less than or equal to 140/80 mm Hg on his regular antihypertensive medication (lisinopril 20 mg) without needing additional therapy. Furthermore, the patient was regularly reviewed by the physiotherapy and occupational therapy teams for rehabilitation support. However, he was not able to engage due to ongoing confusion. Feedback included lethargy, disorientation and poor memory. In addition, he received regular input from the dietitian and speech and language therapy team due to poor and unsafe swallowing.

OUTCOME AND FOLLOW-UP

The patient's admission was complicated by further cognitive decline and fluctuation in conscious level. His GCS level was observed to decline to around 9 (E3 V2 M4) but spontaneously increased to 14 (E4 V4 M6) within the same day. Interim CT brain scan did not reveal any new abnormalities compared with previous scans. This transient reduction in conscious level was thought to be attributable to amyloid 'spells'. However, on one evening, the patient was noted to be

more persistently drowsy than usual. A further CT brain scan was performed, and this revealed a new small focus of bleeding in the brain. The patient's clinical condition continued to deteriorate. After a multidisciplinary discussion that included the patient's family, care was shifted to focus on comfort and palliative measures.

In the weeks following transfer to a hospice, the patient's conscious state appeared to gradually improve again. He was more alert and was able to engage with different allied health professionals, which include dietitians, physiotherapists and occupational therapists. Overall, he is showing good progress in his rehabilitation process. However, the patient's family noted visual impairment that could be explained by the presence of intracerebral microhaemorrhages in the occipital lobe of the brain as seen on the MRI scan (figure 1).

DISCUSSION

Since the emergent of a novel coronavirus named SARS-CoV-2 at the end of 2019, our understanding of the disease caused by it is still very much evolving up to this day. It is increasingly understood that COVID-19 infection is not only limited to the respiratory system, but it can have implications on multiple other organ systems including the nervous system.

In the first COVID-19 study focussing on the effect of the nervous system that was conducted in Wuhan, China, neurological manifestations were found in over one-third of the 214 patients with COVID-19.⁸ Since then, more studies emerged documenting neurological manifestations of COVID-19. In one study, acute cerebrovascular disease (CVD) was present in 5.9% of patients with COVID-19.² Ischaemic stroke is the most frequently reported CVD implicating patients with COVID-19,^{3–5} along with cerebral venous sinus thrombosis,⁶ intracerebral haemorrhage and subarachnoid haemorrhage.^{2 3 7} COVID-19 has been associated with a prothrombotic tendency, which increases the risk of arterial thrombosis leading to acute ischaemic stroke.⁹

Compared with ischaemic stroke, there are significantly fewer cases of haemorrhagic stroke that have been reported in patients with COVID-19. The link between haemorrhagic stroke and COVID-19 infection remains unclear. In most of the previously reported cases of intracerebral haemorrhage, the patients were affected with a more severe form of COVID-19 infection where they required mechanical ventilatory support on critical care.^{2 7} However, our patient did not require any form of respiratory support and did not develop any respiratory symptoms throughout the admission. Sharifi-Razavi *et al* described a case of an elderly man with no known vascular risk factors who presented with massive intracerebral haemorrhage with intraventricular and subarachnoid haemorrhage and concomitant COVID-19 infection.¹⁰ Similar to our patient, they too reported mild infective symptoms before the onset of the neurological symptoms and with lymphopenia and normal CRP, platelet level and clotting parameters. However, MRI brain and CSF analysis were not performed in that patient.

There is only one other case report that described intracerebral haemorrhage associated with CAA in a patient with COVID-19 infection. Fraiman *et al*¹¹ report a case of a 38-year-old patient presenting with first-time intracerebral haemorrhage on a background of CAA who was found to have concomitant COVID-19 infection. She had a medical history of early-onset Alzheimer's disease associated with *amyloid protein precursor* gene duplication. This is known to be associated with the pathogenesis of some cases of CAA.

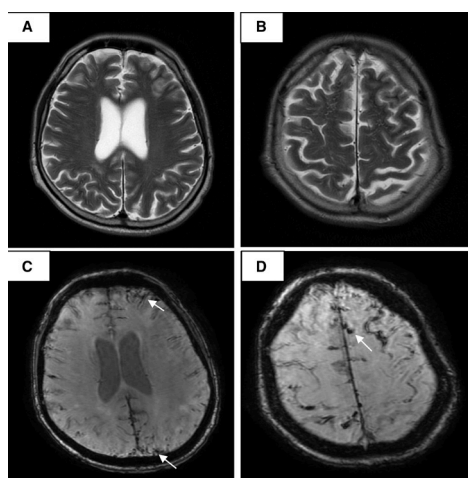


Figure 2 A comparison between T2-weighted (A) and (B) and gradient echo (C) and (D) MRI images from two areas of the brain. These demonstrate microhaemorrhages (white arrows) on the gradient echo with no corresponding oedema on the T2 images.

Contrarily, we describe a case of a previously healthy elderly man presenting with first-time CAA-associated intracerebral haemorrhage and recurrent microbleeds with concurrent COVID-19 infection. CAA is a condition whereby the small to medium blood vessels within the brain are weakened by the deposition of amyloid-beta peptide substance within their walls. This in turn increases the risk of stroke caused by their tendency to bleed.¹² Established risk factors for CAA-associated haemorrhage include genetics, old age, hypertension, anticoagulation and antiplatelet therapy.¹³ Our patient fits the right age group and had well-controlled hypertension but did not possess any of the other risk factors. Importantly, there is also a distinct subtype of CAA that is related to vascular inflammation.¹⁴ The MRI scan appearances of our patient did not suggest this subtype though as this subtype has characteristic inflammatory changes with asymmetrical subcortical areas of ischaemia but these were not present on our patient's MRI. The main radiological abnormality in his case was the excessive number and widespread distribution of microhaemorrhages throughout the brain and brain stem.

It has been suggested that SARS-CoV-2 can cause neuronal damage via direct viral invasion of the nervous system.¹⁵ This in turn can cause a dysregulated neuroimmune response and trigger an inflammatory cascade that generates a cytokine storm with consequent neuroinflammation.¹⁶ We hypothesise that SARS-CoV-2 infection prompted an exaggerated immune response, bringing about increased deposition of congophilic material and further weakening of cerebral vessels already affected by CAA. This consequently led to multiple cerebral microbleeds and resulted in a rapid-onset vascular dementia-type picture as seen in our case. The raised protein and lymphocytic CSF seen in our patient could further point towards an underlying inflammatory process. It is thus conceivable that early administration of anti-inflammatory agents such as steroids might improve clinical outcome. However, our patient described in this case deteriorated secondary to ongoing cerebral microbleeds and subarachnoid haemorrhages rather than due to inflammation; hence, steroid administration was not thought to be beneficial.

CAA is already a known condition with high predisposition for haemorrhage. We are in consensus with Fraiman *et al* that SARS-CoV-2-induced exaggerated inflammatory response might have played a vital role in increasing amyloid-beta peptide deposition in the brain, exacerbating CAA and thereby increasing the risk of haemorrhagic stroke.¹¹

In summary, our patient presented with a clear history of preceding influenza-like symptoms, positive COVID-19 test and negative results for an extensive workup of other possible diagnoses as mentioned above. Thus, we believe COVID-19 infection was contributory to the occurrence of recurrent intracerebral microhaemorrhages by further weakening of the cerebral vessels already damaged by CAA through COVID-19-related vasculopathy. However, more studies need to be conducted to establish or refute the causative relationship between COVID-19 and intracerebral haemorrhage. Nonetheless, our case provides further evidence that COVID-19 could present acutely with cognitive impairment without respiratory symptoms. In this current pandemic, similar clinical presentations should prompt early testing for SARS-CoV-2 to allow for early infection control measures and better protection of our healthcare workers.

Learning points

- ▶ Neurological signs and symptoms may be the first manifestations of COVID-19 infection.
- ▶ Screening for COVID-19 infection is suggested for patients who present with unexplained neurological deficits during the peak of this pandemic.
- ▶ COVID-19 infection can potentially precipitate intracerebral haemorrhage in at-risk patients.
- ▶ There remains limited clinical data to suggest a causative relationship between cerebrovascular accidents and COVID-19 infection. More studies are needed to explain the virus's role in the mechanism of cerebrovascular accidents associated with COVID-19.

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