

Case report

Possible affective cognitive cerebellar syndrome in a young patient with COVID-19 CNS vasculopathy and stroke

Kai Xin Chia,¹ Sonali Polakhare,¹ Stefania Dafne Bruno^{1,2}

¹Blackheath Brain Injury Rehabilitation Centre, London, UK

²IOPPN, King's College London, London, UK

Correspondence to
Dr Stefania Dafne Bruno;
dr.stefania.bruno@gmail.com

Accepted 18 September 2020

SUMMARY

Early case series suggest that about one-third of patients with COVID-19 present with neurological manifestations, including cerebrovascular disease, reported in 2%–6% of hospitalised patients. These are generally older patients with severe infection and comorbidities. Here we discuss the case of a previously fit and well 39-year-old man who presented with fever and respiratory symptoms, evolving in pneumonia with hypoxia but only requiring continuous positive airway pressure. After resolution of the respiratory disease, the patient developed focal neurology and was found to have bilateral occipital, thalamic and cerebellar infarcts. A diagnosis of COVID-19 central nervous system vasculopathy was made. He developed a florid neuropsychiatric syndrome, including paranoia, irritability, aggression and disinhibition, requiring treatment with antipsychotics and transfer to neurorehabilitation. Neuropsychometry revealed a wide range of cognitive deficits. The rapid evolution of the illness was matched by fast resolution of the neuropsychiatric picture with mild residual cognitive impairment.

BACKGROUND

At the time of writing, in September 2020, more than 32 million cases of COVID-19 have been reported, with a global death toll approaching 1 million. COVID-19 is caused by the SARS-CoV-2, a beta-coronavirus with ability to infect humans similar to other viruses from the same group, the SARS-CoV and the Middle East respiratory syndrome coronavirus (MERS-CoV). The known modes of infection are through human to human contact and fomite; possible aerosol transmission in enclosed spaces with poor ventilation has been reported.¹

Electron microscopy studies have suggested that SARS-CoV-2 virus 'spikes' ('S' glycoprotein) act like 'keys' to enter human cells by binding to the ACE2 (ACE2 receptor), similar to other coronaviruses.^{2–5} RNA sequencing studies have determined that ACE2 expression is high in lung, heart, ileum, kidney and bladder^{6,7} as well as brain, vascular endothelium and testis.^{6,8} In the brain the ACE2 receptors have been found in glial cells and neurons, with highest expression in pons and medulla.^{8,9} The ubiquitous presence of ACE2 receptors may explain the multi-organ involvement in COVID-19, which represents a significant difference from other seasonal respiratory

viruses.⁷ Hypercoagulability and excessive systemic inflammatory response in the form of cytokine storm are being recognised as important pathophysiological factors, particularly in severe cases.¹⁰ The main focus of this report is to draw attention to neuropsychiatric presentations of COVID-19-associated cerebrovascular disorder in a young patient.

CASE PRESENTATION

A previously fit and well 39-year-old right-handed information technology engineer of Bangladeshi origin presented in March 2020 with a 9-day history of malaise, fever and cough (day of admission is considered as day 1 for confidentiality purposes). Ambulance staff recorded an oxygen saturation of 85% on room air. On admission he had a respiratory rate of 60 and arterial blood gas (ABG) showed hypoxia with partial pressure of oxygen (PO₂) of 8.87, partial pressure of carbon dioxide of 3.5 and pH of 7.5 on 1 L of oxygen confirming type I respiratory failure. His admission chest X-ray showed peripheral opacities in right middle and left upper and mid zones. His COVID-19 swab came back positive on day 3 though due to pandemic he was treated as probable COVID-19 since admission. He required supplementary oxygen through venture mask for 5–6 days before requiring continuous positive airway pressure for 24 hours due to increasing oxygen demand evident on ABGs with PO₂ of 7.4 with normocapnia. He was quickly weaned off on to venture mask and then on room air on day 8 but developed focal neurology, with reduced Glasgow Coma Scale score, right-sided weakness with hemisensory loss and diplopia. An initial CT of the head was negative for haemorrhage. He was treated with a short 3-day course of methylprednisolone for the possibility of central nervous system (CNS) vasculitis initially raised from the MRI scan.

On day 12 he was referred to liaison psychiatry due to poor engagement in rehabilitation. He was diagnosed with adjustment disorder, started on the antidepressant citalopram and discharged back to the stroke team. He was re-referred to liaison psychiatry 10 days later, when he presented with irritability, aggression and sexual disinhibition. A small dose of olanzapine was started. The contemporary hospital records describe disorientation, distractibility, confabulation, paranoid affect, and verbal and physical aggression. Olanzapine was increased and citalopram was stopped as it was feared that it



© BMJ Publishing Group Limited 2020. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Chia KX, Polakhare S, Bruno SD. *BMJ Case Rep* 2020;13:e237926. doi:10.1136/bcr-2020-237926

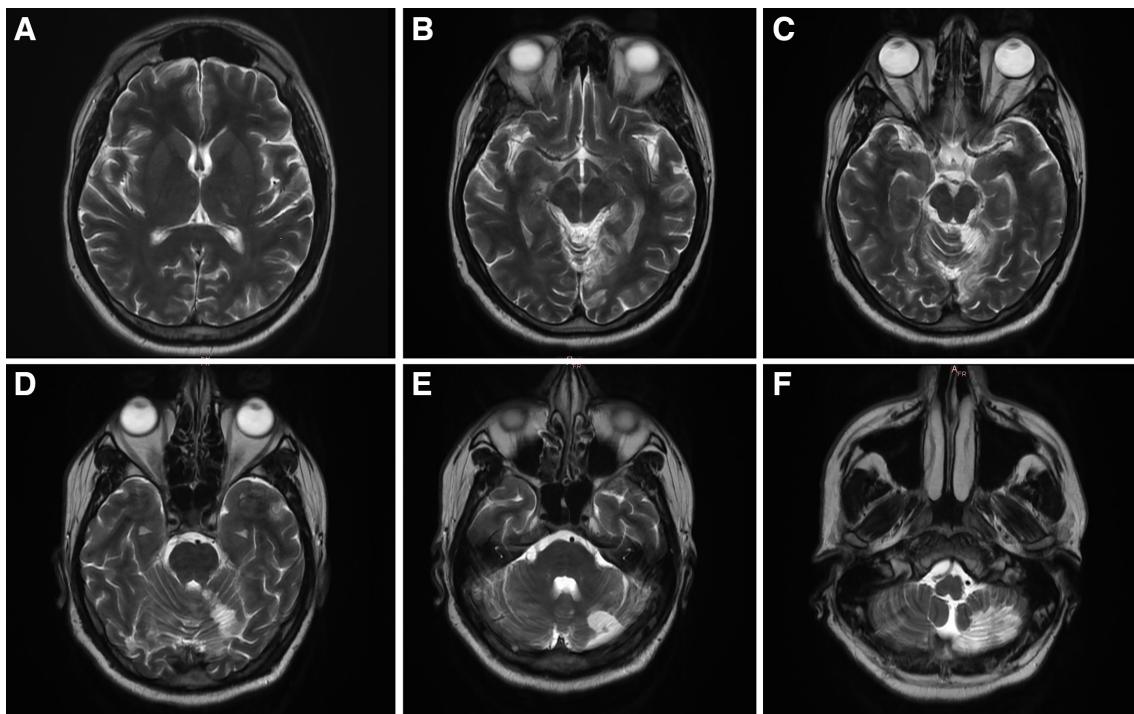


Figure 1 Axial T2 MRIs showing abnormal signal change in the left thalamus, bilateral occipital lobes, cerebellar vermis and left cerebellar hemisphere, due to posterior circulation infarcts.

may have triggered a manic episode. On a Montreal Cognitive Assessment the patient initially scored 12/30, improved to 21/30 after a couple of weeks. He was referred for inpatient intensive neurorehabilitation.

On admission to the neurobehavioural unit, he was well oriented to time and place but his general insight was very limited. Initial cognitive screening indicated significant impairments in attention, processing speed, visuospatial skills, visuospatial construction, verbal fluency, immediate memory, and delayed memory for verbal and visual information.

INVESTIGATIONS

Infection with SARS-CoV-2 was confirmed by reverse transcriptase (RT)-PCR on a nasopharyngeal swab sample on day 3. Blood cultures on admission were negative. He had D-dimer 0.59 (normal level <0.5) on admission which significantly elevated through illness to 2.4 on day 10. CT of the head done on initial neurological presentation showed no acute abnormality. MRI of the brain with gadolinium was reported as showing multiple acute ischaemic infarctions in the territories of the left posterior inferior cerebellar artery and bilateral posterior cerebral arteries (PCAs), implicating the left cerebellar hemisphere, cerebellar vermis, left thalamus and bilateral occipital lobes (figure 1A–F). A possible cardiogenic septic source was ruled out. Trans-thoracic, transoesophageal echocardiogram and bubble echocardiogram were all normal. Cerebral CT angiogram ruled out vascular malformation or intra-arterial thrombus. Magnetic resonance angiography of the neck showed multi-focal areas of narrowing and occlusions in both PCA, especially in the left PCA suggestive of CNS vasculitis probably due to the known COVID-19 viral infection. CT pulmonary angiogram was in keeping with the proved COVID-19 infection without evidence of acute pulmonary embolism.

CT venogram showed no filling defect in the major dural venous sinuses. Lumbar puncture was unremarkable with the exception of mildly raised protein. It was negative for herpes simplex virus (HSV) I and II PCR, enterovirus RNA and varicella zoster. Cerebrospinal fluid could not be tested for SARS-CoV-2 virus at that time in the pandemic.

A battery of standardised neuropsychological tests was administered and the patient's performance was compared with an estimate of his premorbid ability and published UK normative data (table 1). Based on a reading test, the patient's education and occupation history, his premorbid ability was estimated to be at least in the average range.

DIFFERENTIAL DIAGNOSIS

A differential diagnosis of CNS vasculitis versus CNS vasculopathy was discussed at the referring hospital with general specialist consensus in favour of CNS vasculopathy. From the psychiatric point of view, differential diagnoses included a mixed/manic episode precipitated by steroids or by the antidepressant, both unlikely to have contributed significantly due to small doses and brief duration of treatment. The possibility that the presentation may have been explained by delirium was considered (the patient was disorientated) but the psychiatric picture was atypical and described by the assessing consultant psychiatrist as 'manic-like'. Blood and urine confusion screens were negative. There was no evidence of hypoxic brain injury on brain imaging. The pattern of cognitive dysfunction, with deficits in executive functions, visuospatial skills and memory, associated to prominent behavioural changes, raised the possibility of a cerebellar cognitive affective syndrome.¹¹ This has been described in patients with acute lesions of the cerebellum involving the posterior lobe of the cerebellum and the vermis, and it is thought to be due to disruption of

Table 1 Patient's performance on selected cognitive assessments on admission and discharge

	Admission		Discharge	
	SS (percentile)	Classification	SS (percentile)	Classification
Orientation log ²⁵	29/30 ^R	Normal	30/30 ^R	Normal
Repeatable Battery for the Assessment of Neuropsychological Status Update ²⁶				
List learning	5	Borderline	11	Average
Story memory	5	Borderline	12	Average
Figure copy	1	Impaired	1	Impaired
Line orientation	(26th–50th)	Average	(>75th)	Average
Picture naming	(51st–75th)	Average	(51st–75th)	Average
Semantic fluency	3	Impaired	2	Impaired
Digit span	6	Low Average	8	Average
Coding	2	Impaired	5	Borderline
List recall	(≤2nd)	Borderline	(26th–50th)	Average
List recognition	(≤2nd)	Borderline	(≤2nd)	Borderline
Story recall	3	Impaired	7	Low average
Figure recall	1	Impaired	9	Average

The patient scored above the cut-off score on the orientation log (cut-off =>25).

R, raw score; SS, age-adjusted scaled score.

cortico-cerebellar pathways, involving pre-frontal, posterior parietal, temporal and limbic cortex.¹¹

OUTCOME

Within 2 weeks from admission to the neurorehabilitation unit, the patient showed rapid improvements in attention, processing speed and memory, with residual mild to moderate cognitive impairments in executive and visuospatial functions and verbal fluency, and impulsivity. Psychotropic medications were gradually withdrawn and stopped. Functional outcome was evaluated using the UK Functional Independence Measure (FIM) and Functional Assessment Measure (FAM), two instruments designed to measure physical and cognitive/psychosocial disability, respectively, in patients with brain injuries.¹² On admission, the patient scored 104/126 on the FIM and 157/210 on the FAM. At discharge he scored 123/126 on the FIM and 195/210 on the FAM, showing greater improvement in cognitive and psychosocial functions (community mobility could not be assessed due to the pandemic). On discharge the patient was referred and accepted by the local vocational rehabilitation service, which will increase the likelihood of a successful return to his previous occupation. Neuropsychiatric follow-up will not be required.

DISCUSSION

A recent literature review of psychiatric morbidity associated with severe coronavirus infections, which included data on SARS, MERS and COVID-19,¹³ concluded that, in the majority of cases, psychiatric symptoms in coronavirus infections were related either to delirium, or to the psychological sequelae of hospitalisation or contact with a severe infectious disease. The most common symptoms identified were anxiety, depression or post-traumatic stress disorder, with rarer occurrence of neuropsychiatric syndromes.¹³ On the other hand, emerging literature on COVID-19 is increasingly suggesting that neurological involvement is not infrequent, particularly in the more severe cases (see¹⁴ for a review) with encephalopathies, CNS inflammatory syndromes, ischaemic stroke and peripheral neurological disorders recognised as the main categories of disease.¹⁵ The virus is thought to enter the brain through the olfactory bulb, similarly to the HSV.¹⁴ An early case of altered mental state in a patient with acute necrotising encephalopathy with

haemorrhagic lesions was described¹⁶ and related to a cytokine storm syndrome, a condition of hyperinflammation occurring in a subgroup of patients with severe COVID-19.¹⁰ Cerebrovascular events so far have been found in 2%–6% of patients with severe COVID-19 infection.^{14 17 18} While the aetiopathogenesis of cerebrovascular disease in COVID-19 infection is yet to be fully understood, preliminary data suggest that COVID-19 infection may be associated to a state of hypercoagulability. The ACE2 receptor is expressed in the capillary endothelium with roles in capillary formation and vascular homeostasis.¹⁹ Direct viral infection of brain vascular endothelial cells with secondary immune reaction may activate the thrombotic pathway causing microangiopathy.²⁰ Thrombotic events have been observed in patients with COVID-19 despite prophylactic anticoagulation on hospital admission in various large teaching hospitals in the UK European Society of Radiology (ESR) connect webinar 17 May 2020). Significantly raised D-dimers have been detected in up to 36% of patients^{21–23} and have been found to be related to poor outcome. The International Society of Thrombosis and Haemostasis published guidance in March 2020 on admitting patients with positive RT-PCR for SARS CoV-2 if they had raised D-dimer, prolonged prothrombin time, platelets <100×10⁹/L and fibrinogen <2 g/L even in the absence of other clinically

Learning points

- Early brain imaging in COVID-19-positive patients with neuropsychiatric symptoms is of great importance to detect possible cerebrovascular events even in patients outside the 'at risk' group (younger patients without severe respiratory infection or underlying conditions).
- Acute cerebellar lesions may cause a neurobehavioural syndrome requiring psychiatric input and intensive neurorehabilitation.
- Neuropsychological/neuropsychiatric evaluation in patients of working age with COVID-19 with suspected central nervous system involvement is highly desirable to facilitate access to cognitive rehabilitation and vocational therapy, and increase the chances of a successful return to employment.

Lessons learned

concerning features for further monitoring.²⁴ In terms of neuropsychiatric management, referral to specialist services for cognitive neurorehabilitation may be extremely helpful to improve the functional outcome and to ensure access to vocational rehabilitation services and return to work.

Twitter Stefania Dafne Bruno @drstefaniabruno

Contributors KXC and SP have contributed in equal measure to this work. All authors have been involved in the design, planning, drafting and discussion of the article. SDB and SP have been involved in the clinical management of the patient. KXC has carried out the neuropsychometry testing.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

This article is made freely available for use in accordance with BMJ's website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may use, download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

REFERENCES

- 1 Transmission of SARS-CoV-2: implications for infection prevention precautions. WHO/2019-nCoV/Sci_Brief/Transmission_modes/2020.3.
- 2 Li W, Moore MJ, Vasilieva N, et al. Angiotensin-Converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003;426:450–4.
- 3 Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* 2020;367:1260–3.
- 4 Shang J, Ye G, Shi K, et al. Structural basis of receptor recognition by SARS-CoV-2. *Nature* 2020;581:221–4.
- 5 Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181:271–80.
- 6 Hamming I, Timens W, Bulthuis MLC, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004;203:631–7.
- 7 Zou X, Chen K, Zou J, et al. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Front Med* 2020;14:185–92.
- 8 Baig AM, Khaleeq A, Ali U, et al. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci* 2020;11:995–8.
- 9 Lukiw WJ, Pogue A, Hill JM. SARS-CoV-2 infectivity and neurological targets in the brain. *Cell Mol Neurobiol* 2020;1:1–8.
- 10 Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395:1033–4.
- 11 Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. *Brain* 1998;121(Pt 4):561–79.
- 12 Turner-Stokes L, Nyein K, Turner-Stokes T, et al. The UK FIM+FAM: development and evaluation. *Clin Rehabil* 1999;13:277–87.
- 13 Rogers JP, Chesney E, Oliver D, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry* 2020;7:611–27.
- 14 Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. *Lancet Neurol* 2020;19:767–83.
- 15 Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain* 2020;awaa240.
- 16 Poyiadji N, Shahin G, Noujaim D, et al. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: imaging features. *Radiology* 2020;296:201187.
- 17 Fifi JT, Mocco J. COVID-19 related stroke in young individuals. *Lancet Neurol* 2020;19:713–5.
- 18 Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020;77:683–9.
- 19 Lovren F, Pan Y, Quan A, et al. Angiotensin converting enzyme-2 confers endothelial protection and attenuates atherosclerosis. *Am J Physiol Heart Circ Physiol* 2008;295:H1377–84.
- 20 Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endothelitis in COVID-19. *Lancet* 2020;395:1417–8.
- 21 Leonard-Lorant I, Delabranche X, Severac F, et al. Acute pulmonary embolism in COVID-19 patients on CT angiography and relationship to D-dimer levels. *Radiology* 2020;201561.
- 22 Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020;18:844–7.
- 23 Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. *Am J Hematol* 2020;95:834–47.
- 24 Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost* 2020;18:1023–6.
- 25 Jackson WT, Novack TA, Dowler RN. Effective serial measurement of cognitive orientation in rehabilitation: the orientation log. *Arch Phys Med Rehabil* 1998;79:718–21.
- 26 Randolph C. *Repeatable battery for the assessment of neuropsychological status, RBANS update*. Bloomington, MN: NCS Pearson Education, Inc, 2012.

Copyright 2020 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <https://www.bmj.com/company/products-services/rights-and-licensing/permissions/>

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

Customer Service

If you have any further queries about your subscription, please contact our customer services team on +44 (0) 207111 1105 or via email at support@bmj.com.

Visit casereports.bmj.com for more articles like this and to become a Fellow