# COVID-19 encephalitis with SARS-CoV-2 detected in cerebrospinal fluid presenting as a stroke mimic

[*]Diarmuid Glavin MBBS [1], [*]Denise Kelly MBChB [1], [*]Greta Karen Wood MBBS, MRes[2], Beth MS McCausland MBBS[3,4], Mark Alexander Ellul MB BChir[2,5,6], Aravinthan Varatharaj BMBCh, MA (Oxon)[3,4], Ian Galea MD, PhD[3,4], Rhys Huw Thomas MBChB, PhD[7,8], [**]Benedict Daniel Michael MBChB, PhD[2,5,6], [**#]Brian Gallen MB BCh[1]; CoroNerve Study Management Group[***]

1. Department of Stroke Medicine, South West Acute Hospital, Enniskillen, Northern Ireland, UK
2. Department of Clinical Infection Microbiology and Immunology, Institute of Infection, Veterinary, and Ecological Science, Liverpool, UK
3. Clinical Neurosciences, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, UK
4. University Hospital Southampton NHS Foundation Trust, Southampton, UK.
5. Department of Neurology, The Walton Centre NHS Foundation Trust, Liverpool, UK
6. The NIHR Health Protection Research Unit for Emerging and Zoonotic Infection, Liverpool, UK
7. Translational and Clinical Research Institute, Newcastle University, Newcastle, UK
8. Department of Neurology, Royal Victoria Infirmary, Newcastle, UK.

*Joint First Author
**Joint Senior Author
*** Named in acknowledgements
# Corresponding Author

Corresponding author:
Dr Brian Gallen,
South West Acute Hospital,
124 Irvinestown Rd, Enniskillen
BT74 6DN, UK
Email: Brian.Gallen@westerntrust.hscni.net

Diarmuid Glavin. Email: diarmuid.glavin@westerntrust.hscni.net
Denise Kelly. Email: d.kelly6@nhs.net
Greta Karen Wood. Email: greta.wood@liverpool.ac.uk
Beth MS McCausland. Email: beth.mccausland@nhs.net
Mark Alexander Ellul. Email: M.Ellul@liverpool.ac.uk
Aravinthan Varatharaj. Email: A.Varatharaj@soton.ac.uk
Ian Galea. Email: I.Galea@soton.ac.uk
Rhys Huw Thomas. Email: rhys.thomas@newcastle.ac.uk
Benedict Daniel Michael. Email: Benedict.Michael@liverpool.ac.uk

Grant support: This work did not have grant support. Author funding sources are listed under Declaration of Interest.

Running title: COVID-19 encephalitis: potential stroke mimic
Key words: Encephalitis; COVID-19; SARS-Cov-2; Stroke mimic;

Abstract

We report the case of a 35-year-old male with COVID-19 encephalitis presenting as a stroke mimic with sudden-onset expressive and receptive dysphasia, mild confusion and right arm incoordination. The patient received thrombolysis for a suspected ischaemic stroke, but later became febrile and SARS-CoV-2 was detected in cerebrospinal fluid. Electroencephalography demonstrated excess in slow waves, but neuroimaging was reported as normal. Respiratory symptoms were absent throughout and nasopharyngeal swab was negative for SARS-CoV-2. At the most recent follow-up, the patient had made a full neurological recovery. Clinicians should therefore consider testing for SARS-CoV-2 in CSF in patients who present with acute focal neurology, confusion and fever during the pandemic, even when there is no evidence of respiratory infection.

## Introduction

The neurological complications associated with COVID-19 remain under investigation, with cerebrovascular disease at the forefront of debate [1]. This case demonstrates the complexities faced characterising neurological pathology during the SARS-CoV-2 pandemic, with real-world clinical implications.

## Case

A 35-year-old male presented with sudden-onset expressive and receptive dysphasia, mild confusion and right arm incoordination (National Institutes of Health Stroke Scale: 5). The patient had a medical history of migraines only, no regular medication and was a current smoker. Initial CT brain (Fig. 1A) showed no significant intracranial abnormalities and the patient received thrombolysis for a suspected ischaemic stroke. Symptoms resolved over 2 hours and post-thrombolysis CT (day 2, Fig. 1B) was reported as normal. Respiratory symptoms were absent, and admission nasopharyngeal swab was negative for SARS-CoV-2.

On day 3, the patient had right arm weakness and later developed expressive and receptive dysphasia, amnesia, headache and vomiting, followed by pyrexia 39.7 °C. GCS remained 15/15 without evidence of meningism. MRI brain (day 3, Fig. 1C,D) was normal. Lumbar puncture (day 4) had an opening pressure 24cm/$H_2O$ with clear CSF, white cell count 134x$10^6$/L(99% lymphocytes), red cell count 20x$10^6$/L, protein 0.52g/L and CSF:serum glucose ratio 3.7:5.1mmol/L (0.73). CSF culture was negative and polymerase chain reaction (PCR) negative for *Neisseria meningitides*, *Streptococcus pneumoniae* and several viruses including HSV, varicella zoster virus, enterovirus and parechovirus. However, PCR of the CSF was positive for SARS-CoV-2 RNA, with identification of both the E gene (CT value 35.8) and S gene (CT value 35.7) (Altona RealStar SARS-CoV-2 RT-PCR Kit, Roche Flow system). MR angiogram brain (day 5, Fig. 1E) showed incidental congenitally hypoplastic left A1 segment of anterior cerebral artery. Pyrexia and amnesia persisted, but by day 8, the patient was deemed to have made a full recovery and discharged.

Follow-up MRI brain (day 25, Fig. 1F,G) was normal, and electroencephalography (day 34) demonstrated generalized slowing ~~excess in slow waves~~ suggestive of encephalopathy~~itis~~, which was not otherwise explained. At outpatient follow-up (day 55), there were no ongoing neurological symptoms. Serum antibody testing did not detect anti-SARS-CoV-2 antibodies.

## Discussion

The differentiation of strokes and stroke mimics is a particular challenge in COVID-19 patients. Limited stroke risk factors, new seizures, acute or subacute encephalopathy and reduced GCS could suggest a stroke mimic [1].

Whilst several reports have speculated upon the diagnosis of encephalitis in COVID-19 patients, [2-4] detection of SARS-CoV-2 in CSF remains rare [5-7]. Two main plausible routes of entry for SARS-CoV-2 to the central nervous system (CNS) are via the angiotensin-converting enzyme 2 receptors located on epithelial cells of the blood-cerebrospinal fluid barrier and via retrograde axonal transport of peripheral neural pathways such as via the olfactory mucosa in the nasal cavity[8].

Evidence of CSF pleocytosis with white cell count >100 $x10^6$/L is suggestive of CNS infection and is clear evidence of CSF inflammation [9]. Numerous other CNS and systemic infections were excluded on culture and PCR. Non- infectious causes were excluded with brain imaging (CT, MRI and MRA brain). There are several potential reasons for negative nasopharyngeal PCR tests including reduced viral load, transient viral dissemination or collection and storage errors. Research has shown a median false negative rate of COVID-19 nasopharyngeal RT-PCR of 38% on the day of symptom onset and maximum COVID-19 replication in the throat seen 5 days after symptom onset [10-11].

Clinicians should therefore consider testing for SARS-CoV-2 in CSF in patients who present with acute focal neurology, confusion and fever during the pandemic, even when there is no evidence of respiratory infection.

## Declaration

The patient gave consent for publication of his case in the medical literature.

Declaration of interest: None

Funding: IG and AV are supported by NIHR and MRC. BDM is supported to conduct COVID-19 neuroscience research by the UKRI/MRC (MR/V03605X/1); for additional neurological inflammation research due to viral infection BDM is also supported by grants from the MRC/UKRI (MR/V007181//1), MRC (MR/T028750/1) and Wellcome (ISSF201902/3). The funding sources had no role in the writing of this report or decision to submit the article for publication.

Acknowledgements

We would like to acknowledge the Regional Virus Laboratory, Royal Victoria Hospital, Belfast for the diagnostics performed.

CoroNerve Study Group: Rachel Kneen, Sarah Pett, Naomi Thomas, Laura Benjamin, Tom Solomon, Nicholas Davies, Hadi Manji, Ava Easton, Michael Zandi, Jonathan Coles, Craig Smith, David Menon, Tim Nicholson, Beth Tenorio, Victoria Grimbly, Mustafa Sultan, Beth McCausland, Amy Ross Russell, Sarah Crisp, Peter Swann.

References

1. Ellul M, Benjamin L, Singh B et al. Neurological Associations of COVID-19. Lancet Neurol 2020; 19 (9): 767-783

2. Duong L, Xu P, Lu A. Meningoencephalitis without Respiratory Failure in a Young Female Patient with COVID-19 Infection in Downtown Los Angeles, April 2020. Brain, Behav Immun 2020; 87: 33

3. Ye M, Ren Y, Lv T. Encephalitis as a Clinical Manifestation of COVID-19. Brain, Behav Immun 2020. doi.org/10.1016/j.bbi.2020.04.017

4. Al Saiegh F, Ghosh R, Leibold A et al. Status of SARS-CoV-2 in cerebrospinal fluid of patients with COVID-19 and stroke. J Neurol Neurosurg Psychiatry 2020; 91: 846-848.

5. Moriguchi T, Harii N, Goto J et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int Journal Infect Dis 2020; 94: 55-58.

6. Wu Y, Xu X, Chen Z et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain, Behav Immun 2020. 87: 18-22

7. Huang YH, Jiang D, Huang JT. SARS-CoV-2 Detected in Cerebrospinal Fluid by PCR in a Case of COVID-19 Encephalitis. Brain, Behav Immun 2020; 87: 149

8. Koyuncu OO, Hogue IB, Enquist LW. Virus infections in the nervous system. Cell Host Microbe 2013; 13: 379-93.

9. Østergaard, Anne Ahrens et al. "Cerebrospinal fluid pleocytosis level as a diagnostic predictor? A cross-sectional study." *BMC clinical pathology* vol. 17 15. 24 Aug. 2017, doi:10.1186/s12907-017-0053-0

10. Alireza Tahamtan & Abdollah Ardebili (2020) Real-time RT-PCR in COVID-19 detection: issues affecting the results, Expert Review of Molecular Diagnostics, 20:5, 453-454, DOI: 10.1080/14737159.2020.1757437

11. Bahreini, Fatemeh et al. "Reducing False Negative PCR Test for COVID-19." *International journal of MCH and AIDS* vol. 9,3 (2020): 408-410. doi:10.21106/ijma.421

**Figure Legends**

Figure 1: A) Day 1 CT Brain – Normal; B) Day 2 CT Brain- Normal, standard 24-hour post thrombolysis imaging; Day 3 MRI Head T2 (C) and FLAIR (D) – Normal; E) Day 5 MRA Head - normal with congenitally hypoplastic left A1 segment anterior cerebral artery- marked on image (incidental finding) (TOF image); F) Day 25 MRI Head T2 (F) and FLAIR (G) – Normal.

Abstract

We report the case of a 35-year-old male with COVID-19 encephalitis presenting as a stroke mimic with sudden-onset expressive and receptive dysphasia, mild confusion and right arm incoordination. The patient received thrombolysis for a suspected ischaemic stroke, but later became febrile and SARS-CoV-2 was detected in cerebrospinal fluid. Electroencephalography demonstrated excess in slow waves, but neuroimaging was reported as normal. Respiratory symptoms were absent throughout and nasopharyngeal swab was negative for SARS-CoV-2. At the most recent follow-up, the patient had made a full neurological recovery. Clinicians should therefore consider testing for SARS-CoV-2 in CSF in patients who present with acute focal neurology, confusion and fever during the pandemic, even when there is no evidence of respiratory infection.

Introduction

The neurological complications associated with COVID-19 remain under investigation, with cerebrovascular disease at the forefront of debate [1]. This case demonstrates the complexities faced characterising neurological pathology during the SARS-CoV-2 pandemic, with real-world clinical implications.

Case

A 35-year-old male presented with sudden-onset expressive and receptive dysphasia, mild confusion and right arm incoordination (National Institutes of Health Stroke Scale: 5). The patient had a medical history of migraines only, no regular medication and was a current smoker. Initial CT brain (Fig. 1A) showed no significant intracranial abnormalities and the patient received thrombolysis for a suspected ischaemic stroke. Symptoms resolved over 2 hours and post-thrombolysis CT (day 2, Fig. 1B) was reported as normal. Respiratory symptoms were absent, and admission nasopharyngeal swab was negative for SARS-CoV-2.

On day 3, the patient had right arm weakness and later developed expressive and receptive dysphasia, amnesia, headache and vomiting, followed by pyrexia 39.7 °C. GCS remained 15/15 without evidence of meningism. MRI brain (day 3, Fig. 1C,D) was normal. Lumbar puncture (day 4) had an opening pressure 24cm/$H_2O$ with clear CSF, white cell count $134x10^6$/L(99% lymphocytes), red cell count $20x10^6$/L, protein 0.52g/L and CSF:serum glucose ratio 3.7:5.1mmol/L (0.73). CSF culture was negative and polymerase chain reaction (PCR) negative for *Neisseria meningitides*, *Streptococcus pneumoniae* and several viruses including HSV, varicella zoster virus, enterovirus and parechovirus. However, PCR of the CSF was positive for SARS-CoV-2 RNA, with identification of both the E gene (CT value 35.8) and S gene (CT value 35.7) (Altona RealStar SARS-CoV-2 RT-PCR Kit, Roche Flow system). MR angiogram brain (day 5, Fig. 1E) showed incidental congenitally hypoplastic left A1 segment of anterior cerebral artery. Pyrexia and amnesia persisted, but by day 8, the patient was deemed to have made a full recovery and discharged.

Follow-up MRI brain (day 25, Fig. 1F,G) was normal, and electroencephalography (day 34) demonstrated generalized slowing suggestive of encephalopathy, which was not otherwise explained. At outpatient follow-up (day 55), there were no ongoing neurological symptoms. Serum antibody testing did not detect anti-SARS-CoV-2 antibodies.

## Discussion

The differentiation of strokes and stroke mimics is a particular challenge in COVID-19 patients. Limited stroke risk factors, new seizures, acute or subacute encephalopathy and reduced GCS could suggest a stroke mimic [1].

Whilst several reports have speculated upon the diagnosis of encephalitis in COVID-19 patients, [2-4] detection of SARS-CoV-2 in CSF remains rare [5-7]. Two main plausible routes of entry for SARS-CoV-2 to the central nervous system (CNS) are via the angiotensin-converting enzyme 2 receptors located on epithelial cells of the blood-cerebrospinal fluid barrier and via retrograde axonal transport of peripheral neural pathways such as via the olfactory mucosa in the nasal cavity[8].

Evidence of CSF pleocytosis with white cell count >100 $x10^6$/L is suggestive of CNS infection and is clear evidence of CSF inflammation [9]. Numerous other CNS and systemic infections were excluded on culture and PCR. Non- infectious causes were excluded with brain imaging (CT, MRI and MRA brain). There are several potential reasons for negative nasopharyngeal PCR tests including reduced viral load, transient viral dissemination or collection and storage errors. Research has shown a median false negative rate of COVID-19 nasopharyngeal RT-PCR of 38% on the day of symptom onset and maximum COVID-19 replication in the throat seen 5 days after symptom onset [10-11].

Clinicians should therefore consider testing for SARS-CoV-2 in CSF in patients who present with acute focal neurology, confusion and fever during the pandemic, even when there is no evidence of respiratory infection.

## Declaration

The patient gave consent for publication of his case in the medical literature.

Declaration of interest: None

Funding: IG and AV are supported by NIHR and MRC. BDM is supported to conduct COVID-19 neuroscience research by the UKRI/MRC (MR/V03605X/1); for additional neurological inflammation research due to viral infection BDM is also supported by grants from the MRC/UKRI (MR/V007181//1), MRC (MR/T028750/1) and Wellcome (ISSF201902/3). The funding sources had no role in the writing of this report or decision to submit the article for publication.

Acknowledgements

We would like to acknowledge the Regional Virus Laboratory, Royal Victoria Hospital, Belfast for the diagnostics performed.

CoroNerve Study Group: Rachel Kneen, Sarah Pett, Naomi Thomas, Laura Benjamin, Tom Solomon, Nicholas Davies, Hadi Manji, Ava Easton, Michael Zandi, Jonathan Coles, Craig Smith, David Menon, Tim Nicholson, Beth Tenorio, Victoria Grimbly, Mustafa Sultan, Beth McCausland, Amy Ross Russell, Sarah Crisp, Peter Swann.

References

1. Ellul M, Benjamin L, Singh B et al. Neurological Associations of COVID-19. Lancet Neurol 2020; 19 (9): 767-783

2. Duong L, Xu P, Lu A. Meningoencephalitis without Respiratory Failure in a Young Female Patient with COVID-19 Infection in Downtown Los Angeles, April 2020. Brain, Behav Immun 2020; 87: 33

3. Ye M, Ren Y, Lv T. Encephalitis as a Clinical Manifestation of COVID-19. Brain, Behav Immun 2020. doi.org/10.1016/j.bbi.2020.04.017

4. Al Saiegh F, Ghosh R, Leibold A et al. Status of SARS-CoV-2 in cerebrospinal fluid of patients with COVID-19 and stroke. J Neurol Neurosurg Psychiatry 2020; 91: 846-848.

5. Moriguchi T, Harii N, Goto J et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int Journal Infect Dis 2020; 94: 55-58.

6. Wu Y, Xu X, Chen Z et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain, Behav Immun 2020. 87: 18-22

7. Huang YH, Jiang D, Huang JT. SARS-CoV-2 Detected in Cerebrospinal Fluid by PCR in a Case of COVID-19 Encephalitis. Brain, Behav Immun 2020; 87: 149

8. Koyuncu OO, Hogue IB, Enquist LW. Virus infections in the nervous system. Cell Host Microbe 2013; 13: 379-93.

9. Østergaard, Anne Ahrens et al. “Cerebrospinal fluid pleocytosis level as a diagnostic predictor? A cross-sectional study.” *BMC clinical pathology* vol. 17 15. 24 Aug. 2017, doi:10.1186/s12907-017-0053-0

10. Alireza Tahamtan & Abdollah Ardebili (2020) Real-time RT-PCR in COVID-19 detection: issues affecting the results, Expert Review of Molecular Diagnostics, 20:5, 453-454, DOI: 10.1080/14737159.2020.1757437

11. Bahreini, Fatemeh et al. “Reducing False Negative PCR Test for COVID-19.” *International journal of MCH and AIDS* vol. 9,3 (2020): 408-410. doi:10.21106/ijma.421

**Figure Legends**

Figure 1: A) Day 1 CT Brain – Normal; B) Day 2 CT Brain- Normal, standard 24-hour post thrombolysis imaging; Day 3 MRI Head T2 (C) and FLAIR (D) – Normal; E) Day 5 MRA Head - normal with congenitally hypoplastic left A1 segment anterior cerebral artery- marked on image (incidental finding) (TOF image); F) Day 25 MRI Head T2 (F) and FLAIR (G) – Normal.

Figure(s)

Click here to access/download;Figure(s);Figure1- COVID19 stroke mimic JSCVD 290421.pptx