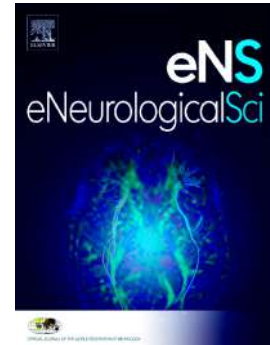


Journal Pre-proof

Post-COVID seizure: A new feature of “long-COVID”

Keith J. Kincaid, Justin ChiKung, Alexander J. Senetar, David Mendoza, Daniel A. Bonnin, Windy L. Purtlebaugh, Rainier M. Cabatbat, Rondalyn Dickens, Franklin D. Echevarria, Vidhu Kariyawasam, Maria Bruzzone, Alexis N. Simpkins



PII: S2405-6502(21)00032-0

DOI: <https://doi.org/10.1016/j.ensci.2021.100340>

Reference: ENSCI 100340

To appear in: *eNeurologicalSci*

Received date: 31 January 2021

Revised date: 5 April 2021

Accepted date: 12 April 2021

Please cite this article as: K.J. Kincaid, J. ChiKung, A.J. Senetar, et al., Post-COVID seizure: A new feature of “long-COVID”, *eNeurologicalSci* (2021), <https://doi.org/10.1016/j.ensci.2021.100340>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier B.V.

Post-COVID Seizure: A New Feature of “Long-COVID”

Keith J Kincaid*,^a Justin ChiKung*,^b Alexander J Senatar*,^c David Mendoza,^d Daniel A Bonnin,^e Windy L Purtlebaugh,^f Rainier M Cabatbat,^g Rondalyn Dickens,^h Franklin D Echevarria,ⁱ Vidhu Kariyawasam,^j Maria Bruzzone,^k Alexis N Simpkins^l

* These authors contributed equally to the creation of this manuscript.

^a Keith J Kincaid, MD, University of Florida, Department of Neurology, Gainesville, Florida, USA. Email: keith.kincaid@neurology.ufl.edu. Phone: 352-273-5550.

^b Justin Chi Kung, University of Florida, Department of Neurology, Gainesville, Florida, USA. Email: justin.kung@ufl.edu. Phone: 352-273-5550.

^c Alexander J. Senatar, DO, University of Florida, Department of Neurology, Gainesville, Florida, USA. Email: alexander.senatar@neurology.ufl.edu. Phone: 352-273-5550.

^d David Mendoza, MD, University of Florida, Department of Neurology, Gainesville, Florida, USA. Email: david.mendoza@neurology.ufl.edu. Phone: 352-273-5550.

^e Daniel A. Bonnin, MD, MS, University of Florida, Department of Neurology, Gainesville, Florida, USA. Email: Daniel.bonnin@neurology.ufl.edu. Phone: 352-273-5550.

^f Windy L Purtlebaugh, BSN, FNP-BC, University of Florida, Department of Neurology, Gainesville, Florida, USA. Email: Purtlebaugh.Windy@shands.ufl.edu. Phone: 352-273-5550.

^g Rainier M. Cabatbat, MD, MS Medstar Washington Hospital Center, Comprehensive Stroke Center, Washington, District of Columbia, USA. Email: rainiermrc@gmail.com. Phone: 714-343-9247.

^h Rondalyn Dickens, MS, University of Florida, Department of Neurology, Gainesville, Florida, USA. Email: rdickens@ufl.edu. Phone: 352-273-5550.

ⁱ Franklin D. Echevarria, PhD, University of Florida, Department of Neurology, Gainesville, Florida, USA. Email: franklin.echevarria@neurology.ufl.edu. Phone: 352-273-5550.

^j Vidhu Kariyawasam, MD, University of Florida, Department of Infectious Disease, Gainesville, Florida, USA. Email: vidhu.kariyawasam@medicine.ufl.edu. Phone: 352-273-5550.

^k Maria Bruzzone, MD, University of Florida, Department of Neurology, Gainesville, Florida, USA. Email: maria.bruzzonegiraldez@neurology.ufl.edu. Phone: 352-273-5550.

^l Alexis N. Simpkins, MD, PhD, MSCR. Department of Neurology, University of Florida, Gainesville, USA. Email: alexis.simpkins@neurology.ufl.edu. Phone: 352-273-5550.

Institution: All work was performed in collaboration between the Department of Neurology and Department of Infectious Disease at the University of Florida.

Grant Support: None

Corresponding Author:

Alexis N. Simpkins, MD, PhD, MSCR
1149 Newell Drive, Rm. L3-100
Gainesville, FL 32611

Phone: 352-273-5550

Fax: 352-273-5575

Alexis.simpkins@neurology.ufl.edu

Abstract

Novel coronavirus SARS-CoV-2 has created unprecedented healthcare challenges. Neurologic deficits are often an important presenting symptom. To date, the only reported post-infectious COVID-19 manifestations of neurologic disease include cognitive deficits and dysfunction of the peripheral nervous system. Here we report that seizure can also be a post-COVID-19 or “long-COVID” complication. We present a 71-year-old man with hypertension, diabetes mellitus, and COVID-19 diagnosed by RT-PCR who initially presented with posterior circulation stroke-like symptoms, which completely resolved after emergent thrombolysis. Six days later, the patient returned with seizure activity, supported by radiographic and electroencephalographic studies. Notably, he was negative for SARS-CoV-2, and no other provoking factor was uncovered after a comprehensive work-up. To our knowledge, this is the first report of post-infectious seizures after a case of COVID-19, highlighting the potential importance of monitoring for neurologic symptoms in COVID-19 patients, even after convalescence.

Keywords: COVID-19; Stroke; Seizure; SARS-CoV-2, Long-COVID; post-infectious seizure

Case Description

A 71-year-old man with hypertension and diabetes mellitus presented to emergency services within three hours of witnessed sudden onset dysconjugate gaze, ptosis, vertical diplopia, nausea, and vomiting. Computed tomography (CT) angiography with perfusion imaging was remarkable for severe right vertebral artery stenosis and normal perfusion (Figure A). Shortly after thrombolysis administration, all symptoms resolved. An RT-PCR test for SARS-CoV-2 was positive on admission, and mild interstitial pulmonary disease was evident on chest x-ray in the absence of respiratory symptoms. Additional work-up, including stroke labs, echocardiography, and cardiac telemetry, was otherwise unremarkable. He was discharged home without neurological deficits. Six days later, the patient was found confused and incontinent by family members and was emergently returned to the hospital. Repeat CT angiography with perfusion demonstrated new hyperemia in the bilateral frontal lobes suggestive of recent seizure (Figure 1A). Electroencephalogram (EEG) captured several seizures manifesting as lateralized, right central predominant, sharply-contoured rhythmic delta activity at 1-3 Hz that spread to the temporal, then frontal lobes bilaterally (Figure B 1-4). On this admission, repeat testing for SARS-CoV-2 virus using the same PCR platform and testing protocol was negative. Contrast-enhanced magnetic resonance imaging (MRI) of the brain was unrevealing (Figure C). Studies to evaluate for toxic, metabolic, inflammatory, and infectious processes from serum and cerebrospinal fluid were unremarkable only for the patient's known mild chronic hyponatremia, which was stable from labs dating back three years (Table 1). The patient's seizures were managed with intravenous loading of anti-epileptics. He ultimately required both phenytoin and levetiracetam, but he returned to his neurologic baseline after achieving therapeutic anti-epileptic drug levels and was discharged home.

Discussion

To our knowledge, this is the first report of a COVID-19 patient whose presenting symptoms were primarily neurological without clinically significant respiratory disease and who later returned during the convalescent period of COVID-19 with seizures unexplained by other identifiable causes. It is believed

that the patient's initial presentation was a thrombolysis-aborted posterior circulation stroke or transient ischemic attack given reasonable clinical suspicion and severe vertebral artery stenosis. Furthermore, the patient's deficits rapidly resolved after thrombolysis and were not accompanied by confusion or memory loss. Thus, these clinical symptoms from the first admission were more consistent with a cerebrovascular etiology. MRI of the brain was negative; however, it's worth noting that infarcts in the posterior circulation territory can be missed on MRI, particularly if they are small in size.¹ The patient's return presentation was consistent with seizure, both subjectively and objectively. CT perfusion images obtained during the second presentation on the same CT scanner using the same imaging protocol produced characteristic features of seizure such as increased cerebral blood flow to the frontal lobes later correlated with areas of epileptiform activity on EEG. While it is possible that the patient's two presentations reflect a singular progressive neurologic disorder, the imaging and clinical presentations suggest otherwise.^{2,3} Both stroke and seizure have independently been associated with COVID-19.^{3,4,5,6,7,8,9}

In the initial study from Wuhan, China 214 patients with COVID-19 revealed neurological complications in 36%, the most common being ischemic stroke.⁷ Multiple factors contribute to neurological manifestations in COVID-19, such as COVID-19 coagulopathy, endothelial cell dysfunction, and thrombosis. Still, the precise causative mechanisms for COVID-19 associated neurologic manifestations are unclear.^{10,11} The association between stroke and COVID-19, in particular, is thought to be caused by SARS-CoV-2 triggered inflammation and thrombosis.¹² Others have previously reviewed the association between COVID-19 and stroke,¹² so the case discussion here will focus on the association between COVID-19 and seizure and "long-COVID" neurologic symptoms.

The mechanisms behind COVID-19 associated seizure are also not fully understood.^{13,14} A growing number of studies have reported a possible association between seizures and COVID-19 through multiple pathways, including direct neuroinvasion of the SARS-CoV-2 virus via olfactory neuron axonal transport and hematogenous spread via disruption of the blood brain barrier.^{15,16,17} Other indirect factors may also contribute to the cause of seizures in COVID-19, including features such as hypoxia, multiorgan failure, and metabolic derangements typically seen in severe disease.^{14,18,19} Of growing concern are reports that there may be an association between in-hospital mortality and new-onset seizures with COVID-19 infection, such as in our patient.^{20,21}

Altogether, compelling questions are raised by this case of "long-COVID" seizures. It suggests that manifestations of COVID-19 may occur during convalescence when SARS-CoV-2 mRNA is no longer detectable by RT-PCR. "Long COVID" neurological symptoms to date have included primarily cognitive deficits and neuromuscular disorders.^{22,23,24} This case is the first report of post-COVID-19 seizures. We postulate that the post-infectious neurologic complications of prior COVID-19 infection are likely a consequence of lingering inflammation and upregulated cytokines within the central nervous system. This case also suggests that investigating for previous COVID-19 infections may be useful in the work-up of new onset neurologic disease such as seizures, especially during the pandemic in a patient with new onset neurologic disorder with no other identified etiology.

Diagnosing "long-COVID" complications of COVID-19 does present diagnostic challenges. Patients previously diagnosed with COVID-19, such as the patient we presented, can be tracked longitudinally. It is important to note that our patient did not have respiratory symptoms and thus was not diagnosed early during his infection. As a result, patients with mild disease may not be diagnosed with COVID-19 prior to presentation with a neurologic disorder in the "long-COVID" phase. It's believed that the SARS-CoV-2 RT-PCR test was likely negative on the second presentation because the patient was at the later phase of the SARS-CoV-2 infection, and thus fully cleared the infection by the time of the second presentation. The mRNA sequences used for RT-PCR testing are highly specific based on the unique genetic sequences of SARS-CoV-2.²⁵ At our institution, COVID-19 antibody testing is not routinely performed since RT-PCR testing is more reliable. However, in the absence of other diagnostic tools, it may be useful to also

test for antibodies that could suggest prior COVID-19 disease as part of the diagnostic work-up of new-onset neurologic disorders of unclear origin.^{25,26}

Given the paucity of longitudinal data on patients with neurologic manifestations of COVID-19, patients should be followed closely even if it appears they did not have severe manifestations of COVID-19 or are no longer testing SARS-CoV-2 positive. Future studies examining the relationship between mild COVID-19 symptomatology and “Long-COVID” neurologic symptoms may be informative.

Disclosure statement

None of the authors had any reported conflicts of interest.

Figure/Table Captions and Legends

Table 1

Initial Hospital Presentation	Second Presentation
SARS-CoV-2 RT-PCR Test Results	
SARS-CoV-2 PCR test positive	SARS-CoV-2 PCR test negative
Additional Abnormal Labs	
Serum Labs: C-reactive protein - 15.7 Vitamin D 25 – 41 Sodium - 133	Serum Labs: Sodium - 135
Normal or Negative Additional Labs	
Serum Labs: WBC - 8.8 Hemoglobin - 15 g/dL Platelet count - 409 INR - 1.0 PT - 12 PTT - 28 Fibrinogen - 365 D-dimer - 0.43 Total cholesterol - 104 HDL - 33 LDL calculated - 55 A1c - 6.3% TSH - 0.269 Vitamin B12 - 515 Ethyl alcohol - 10 Phosphatidylethanol - Negative	Serum Labs: WBC 9.9 Hemoglobin 11.1 Platelet count 348 INR 1.1 aPTT -28 Rheumatoid factor - <10 ANCA - negative ACE - <5 dsDNA - negative Scl 70 - negative Ribonucleic protein IgG - negative Smith - negative SSB - negative SSA -negative Arbo panel - negative ANA - negative Vitamin B1 - 353

	Ammonia – Normal Serial Troponins – Normal Cerebral Spinal Fluid labs: CSF WBC - 2 CSF RBC - 0 CSF glucose - 92 CSF protein - 39 HSV CSF - Negative entero - negative Blastomyces - negative Histoplasma - negative Blood cultures (from 4/26) - negative Cytometry - no evidence of monoclonal B-cell population Cryptococcal - negative MBP - negative VDRL - negative lyme - negative OCB - negative CSF ACE - 0.5 EBV - negative VZV - negative CMV - negative Cytology - no evidence of malignancy Coccidioides - negative CSF albumin - 16 HIV - negative CSF culture - negative AFB - negative fungal Culture - negative
--	--

Figure 1. Radiographic and electrographic data.

There was no perfusion deficit on initial presentation as depicted by the mean transit and time to peak perfusion maps to the left (A), but on the second admission, the patient had hyperemia in bilateral frontal lobes suggestive of recent seizure activity depicted by the perfusion maps on the right which have more blue on the maps (blue areas indicate faster time intervals) in bilateral frontal lobes on both perfusion maps (A). EEG revealed lateralized, right central predominant, sharply-contoured rhythmic delta activity at 1-3 Hz that spread to the temporal, then frontal lobes bilaterally (B 1-4). MRI imaging confirmed chronic small vessel ischemic changes, but no stroke or abnormal patterns of enhancement as depicted by the post contrast fluid attenuated recovery sequence (C).

References

1. Nouh A, Remke J, Ruland S. Ischemic posterior circulation stroke: a review of anatomy, clinical presentations, diagnosis, and current management. *Front Neurol.* 2014;5:30.
2. Kandemirli SG, Dogan L, Sarikaya ZT, et al. Brain MRI Findings in Patients in the Intensive Care Unit with COVID-19 Infection. *Radiology.* 10 2020;297(1):E232-E235.
3. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. *ACS Chem Neurosci.* Apr 1 2020;11(7):995-998.
4. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol.* 06 2020;77(6):683-690.
5. Herman C, Mayer K, Sarwal A. Scoping review of prevalence of neurologic comorbidities in patients hospitalized for COVID-19. *Neurology.* 07 2020;95(2):77-84.
6. Sohal S, Mansur M. COVID-19 Presenting with Seizures. *IDCases.* 2020;20:e00782.
7. Beyrouti R, Adams ME, Benjamin L, et al. Characteristics of ischemic stroke associated with COVID-19. *J Neurol Neurosurg Psychiatry.* 08 2020;91(8):889-891.
8. Merkler AE, Parikh NS, Mir S, et al. Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs Patients With Influenza. *JAMA Neurol.* Jul 2020.
9. Josephson SA, Kamel H. Neurology and COVID-19. *JAMA.* 05 2020;324(12):1139-1140.
10. Perry RJ, Smith CJ, Roffe C, et al. Characteristics and outcomes of COVID-19 associated stroke: a UK multicentre case-control study. *J Neurol Neurosurg Psychiatry.* Nov 2020.
11. Gutierrez Amezcua JM, Jain R, Kleinman G, et al. COVID-19-Induced Neurovascular Injury: a Case Series with Emphasis on Pathophysiological Mechanisms. *SN Compr Clin Med.* 2020;2(11):2109-2125.
12. Leira EC, Russman AN, Biller J, et al. Preserving stroke care during the COVID-19 pandemic: Potential issues and solutions. *Neurology.* Jul 21 2020;95(3):124-133.
13. Elgamasy S, Kamel MG, Ghozy S, Khalil A, Morra ME, Islam SMS. First case of focal epilepsy associated with SARS-coronavirus-2. *J Med Virol.* 10 2020;92(10):2238-2242.
14. Hogan RE, Grinspan Z, Axteen E, Marquis B, Day BK. COVID-19 in Patients With Seizures and Epilepsy: Interpretation of Relevant Knowledge of Presenting Signs and Symptoms. *Epilepsy Curr.* Sep 2020;20(5):312-315.
15. Alquisiras-Burgos I, Peralta-Arrieta I, Alonso-Palomares LA, Zacapala-Gómez AE, Salmerón-Bárceñas EG, Aguilera P. Neurological Complications Associated with the Blood-Brain Barrier Damage Induced by the Inflammatory Response During SARS-CoV-2 Infection. *Mol Neurobiol.* Feb 2021;58(2):520-535.
16. Kumari P, Rothan HA, Natekar JP, et al. Neuroinvasion and Encephalitis Following Intranasal Inoculation of SARS-CoV-2 in K18-hACE2 Mice. *Viruses.* 01 2021;13(1).
17. Lee MH, Perl DP, Nair G, et al. Microvascular Injury in the Brains of Patients with Covid-19. *N Engl J Med.* Dec 2020.
18. Somani S, Pati S, Gaston T, Chitlangia A, Agnihotri S. De Novo Status Epilepticus in patients with COVID-19. *Ann Clin Transl Neurol.* Jul 2020;7(7):1240-1244.
19. Nikbakht F, Mohammadkhanizadeh A, Mohammadi E. How does the COVID-19 cause seizure and epilepsy in patients? The potential mechanisms. *Mult Scler Relat Disord.* Nov 2020;46:102535.
20. Sun M, Ruan X, Li Y, et al. Clinical characteristics of 30 COVID-19 patients with epilepsy: A retrospective study in Wuhan. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases.* 2020:S1201-9712(1220)32191-32193.

21. Cabezudo-García P, Ciano-Petersen NL, Mena-Vázquez N, Pons-Pons G, Castro-Sánchez MV, Serrano-Castro PJ. Incidence and case fatality rate of COVID-19 in patients with active epilepsy. *Neurology*. 09 2020;95(10):e1417-e1425.
22. Novak P. Post COVID-19 syndrome associated with orthostatic cerebral hypoperfusion syndrome, small fiber neuropathy and benefit of immunotherapy: a case report. *eNeurologicalSci*. Dec 2020;21:100276.
23. Heneka MT, Golenbock D, Latz E, Morgan D, Brown R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. *Alzheimers Res Ther*. 06 2020;12(1):69.
24. Wijeratne T, Crewther S. Post-COVID 19 Neurological Syndrome (PCNS); a novel syndrome with challenges for the global neurology community. *J Neurol Sci*. 12 2020;419:117179.
25. Ndwandwe D, Mathebula L, Kamadjeu R, Wiysonge CS. Cochrane corner: rapid point-of-care antigen and molecular-based tests for the diagnosis of COVID-19 infection. *Pan Afr Med J*. 2020;37(Suppl 1):10.
26. Wise J. Covid-19: Timing is critical for antibody tests, finds Cochrane review. *BMJ*. Jun 25 2020;369:m2584.

Highlights for review

- Patients with COVID-19 can develop multiple neurologic disorders
- Seizure can be a manifestation of the “Long-COVID” syndrome.
- Longitudinal studies of neurologic disease in COVID-19 survivors are needed.

Publication History: None

Financial Disclosures: None

Conflict of Interest: None

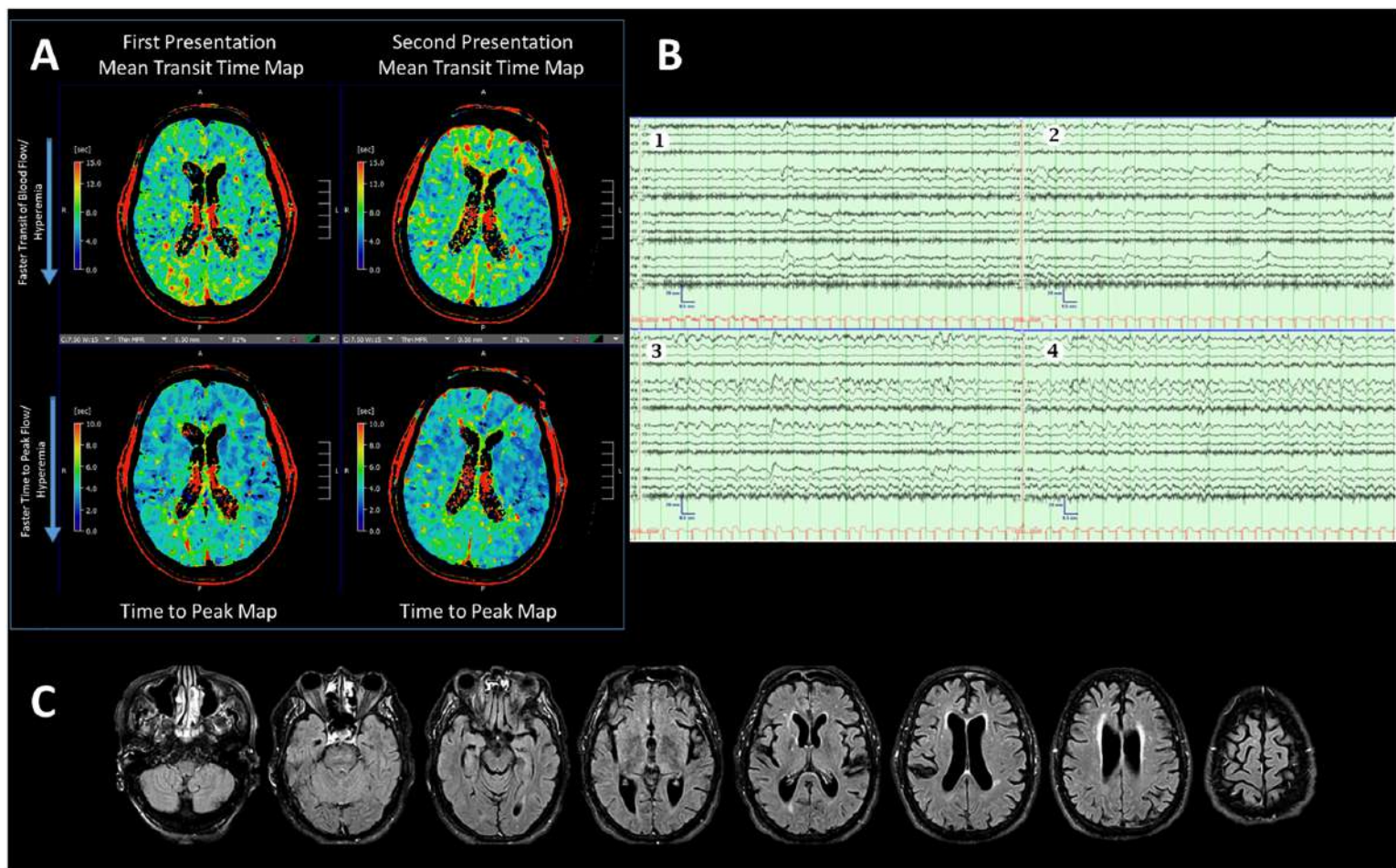


Figure 1