



## Case report

# Therapeutic plasma exchange for persistent encephalopathy associated with Covid-19



Chakrapani Ranganathan<sup>a,\*</sup>, Shelley D. Fusinski<sup>a</sup>, Imad M. Obeid<sup>b,\*\*</sup>, Khaled M. Ismail<sup>c,\*\*</sup>, Derrick T. Ferguson<sup>b</sup>, Mindy F. Raminick<sup>c</sup>, Sean M. Dawes<sup>b</sup>

<sup>a</sup> Ascension Macomb-Oakland Hospital, Neurology, USA

<sup>b</sup> Ascension Macomb-Oakland Hospital, Pulmonary/Critical Care Medicine, USA

<sup>c</sup> Ascension Macomb-Oakland Hospital, Nephrology, USA

## ABSTRACT

Patients infected with COVID-19 virus, show a highly variable symptomatology which can include central nervous system (CNS) dysfunction. One of the most disabling CNS manifestations is persistent severe encephalopathy seen for weeks after the resolution of the acute viral pneumonia and associated acute systemic illnesses. The precise pathophysiology of this persistent Post COVID Encephalopathy is unknown but may involve direct viral invasion of microvascular endothelium, microvascular thrombosis, toxic neuronal effects of inflammatory products, vasoactive pathology at arteriolar level or leptomeningeal inflammation. Currently, there are no established specific treatments for Post COVID -19 encephalopathy. We present a case series of three patients that underwent Therapeutic Plasma Exchange (TPE) with salinized albumin that suggests a positive therapeutic effect. We believe that the results warrant further evaluation for the role of TPE with a prospective randomized trial in persistent Post COVID -19 encephalopathy syndrome.

## 1. Introduction

In addition to the well-described respiratory manifestations of COVID-19 infection, there are central nervous system symptoms that are increasingly recognized and may affect more than one-third of infected patients [1,8]. Severe reduction in the level of consciousness, headache, anosmia, paresthesia, disorientation, inattention and ataxia are some of the commonly reported symptoms associated with Covid-19 encephalopathy [1,10,12]. The etiology for encephalopathy during the acute phase of Covid-19 infection is likely multifactorial. However, the etiology for the persistent encephalopathy after resolution of the acute infectious phase, respiratory failure, acute respiratory distress syndrome (if present), concomitant superinfection and metabolic derangements is not entirely known. Current theories include continued coagulopathy associated with elevated D-Dimer, a direct neuro-invasive viral process, endothelialitis associated with COVID -19 infection and/or post-infectious autoimmune mechanisms [15]. Brain imaging findings of patients with Covid-19 encephalopathy have not been consistent but some studies have found leptomeningeal enhancement and/or bilateral frontotemporal hypoperfusion [3,10]. The cerebrospinal fluid analyses, when reported, have mostly shown non-specific findings with occasional oligoclonal bands and/or elevated IgG levels [6]. However, SARS-CoV-2

RNA particles have been isolated in the cerebrospinal fluid suggesting possible direct neuronal infection [18]. Most EEG studies are reported as showing non-specific changes associated with encephalopathy and rarely have shown epileptiform or interictal patterns [7]. Therapeutic Plasma Exchange (TPE) is an apheresis process during which the patient's plasma component is separated from the blood, via centrifugation, and replaced with salinized albumin. TPE has been successfully used as a therapy for neurological conditions such as Guillain-Barre syndrome, Myasthenia Gravis and Chronic Inflammatory Demyelinating Polyneuropathy [16]. A more recent trial found TPE to be a safe and effective alternative in patients with steroid-responsive encephalopathy and limbic encephalitis [17]. On the premise of the prior studies and proposed mechanisms for post Covid-19 encephalopathy, TPE was provided in three cases in an effort to try reverse this disabling CNS pathology.

## 2. Cases

The first case is a 69-year-old black female with past medical history of coronary artery disease, hypertension, diabetes mellitus, obesity, dyslipidemia and recently diagnosed chronic myeloid leukemia for which she was initiated on Imatinib. She presented to hospital with a

\* Corresponding author at: 27427 Schoenherr Rd #100, Warren, MI 48088, USA.

\*\* Corresponding authors.

E-mail address: [chakrapani.ranganathan@ascension.org](mailto:chakrapani.ranganathan@ascension.org) (C. Ranganathan).

<https://doi.org/10.1016/j.ensci.2021.100327>

Received 20 January 2021; Accepted 5 February 2021

Available online 7 February 2021

2405-6502/© 2021 The Authors.

Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

five-day history of fevers, diarrhea, generalized weakness and worsening dyspnea but no specific behavioral or cognitive symptoms. She was subsequently confirmed to be positive for Covid-19 infection via Nasopharyngeal swab PCR testing. Initial laboratory testing, which consisted of complete blood count, basic metabolic panel, hepatic function panel and inflammatory markers, revealed mostly normal values with the exception of mild thrombocytopenia (144 K/mcL), mildly elevated serum creatinine (2.25 mg/dL), mildly decreased serum bicarbonate (19 mEq/L) and elevated markers of inflammation (D-Dimer of 820µg/mL, Ferritin 276 ng/mL and C-reactive protein of 67.4 mg/L). Initial Chest X Ray showed a pattern of bilateral patchy infiltrates consistent with Covid-19 pneumonia. Despite initiation of the standard therapy at that time, of Hydroxychloroquine and Methylprednisolone, her respiratory status progressively worsened requiring endotracheal intubation and mechanical ventilatory support. She remained on mechanical ventilatory support for more than thirty days during which time her serum creatinine normalized but her inflammatory markers remained elevated and culminated in her requiring a tracheostomy. On the twenty fifth day of her admission, neurology was consulted to evaluate for persistent encephalopathy and the inability to wean her from the ventilator despite optimization of her pulmonary status. Initial neurological evaluation found her to be unresponsive to verbal stimuli and only weakly withdrawing her limbs to brief noxious stimuli. Brainstem responses including doll's eye, corneal and gag reflexes were intact with the exception of pupillary response to bright light stimulus. There was no posturing nor motor behavior suggestive of epileptic activity. Computed tomographic (CT) imaging of her brain did not reveal evidence of an acute intracranial process. Subsequent electroencephalograms (EEG) demonstrated an alpha coma pattern with a non-reactive rhythm and no epileptiform patterns. No significant prior hypotensive events, no evidence of persistent bacterial infections and no significant metabolic abnormalities were found to explain her persistent severe encephalopathy, at this time. Her medication records were also reviewed. A low dose of fentanyl infusion was being given for analgesia while on mechanical ventilation. All sedating or analgesic medications were subsequently held and this resulted in no improvement in mentation. At this point the patient's family was contemplating a transition to hospice care but asked for anything else experimental as a palliative measure to wake her up. Therapeutic plasma exchange (TPE) was considered as an experimental option with the family. After discussion of the potential risks and unknown benefits of TPE, an informed consent was obtained. The TPE was initiated on every other day regimen over ten days, totaling five exchanges. A mild improvement in mentation was noticeable after a single session of TPE. Significant improvement was noted in mentation with subsequent sessions. She began following one step simple commands, then improved to following multiple simple commands and finally began mouthing words. After initiation of TPE, improvement was documented on her EEG as well. The first EEG after starting TPE showed a reactive background rhythm. The subsequent EEG showed a reactive 8 Hz alpha rhythm with milder diffuse polymorphic theta delta activity. The markers of inflammation decreased rapidly with each TPE to normal range. She was subsequently determined to be clinically stable and discharged to a long-term acute care facility.

The second case is a 66-year-old Caucasian male who tested positive in Covid-19 PCR screening and presented with obtundation with worsening hypoxemia refractory to non-invasive therapy. Initial point of care blood glucose was noted to be 73 mg/dL for which he was given one 50 mL ampule of 50% dextrose solution intravenously without improvement in his mentation despite correction of serum glucose level. He was subsequently intubated and placed on mechanical ventilatory support and given Methylprednisolone, Remdesivir and anticoagulant dose of intravenous Heparin (for elevated D-Dimer >3000µg/mL). Further work-up yielded positive urine and sputum cultures for *Klebsiella pneumoniae* and *Corynebacterium striatum* respectively. He was treated with appropriate antibiotics for these pathogens. Despite optimization of his

metabolic, respiratory and hemodynamic statuses he remained encephalopathic. Neurological evaluation was requested for further management of his impaired mental state with ventilator dependency. The first neurologic assessment revealed that the patient was unresponsive to verbal stimuli and only exhibited weak withdrawal to noxious stimulus. During this initial evaluation the patient was noted to have episodic tonic vertical gaze deviation raising concern for seizure. A stat EEG demonstrated a slow disorganized alpha rhythm at 7 Hz with moderately increased polymorphic theta delta activity bilaterally with slight right sided predominance and several brief clusters of sharp waves over the right hemisphere. Since the patient was already on a low dose of valproate sodium for other indications, the dosage was increased to raise the Valproate serum levels to therapeutic range for seizure disorder. As part of the work-up for his encephalopathy, imaging studies were obtained. Non-contrast CT Brain did not reveal any acute intracranial process but did reveal a pattern suggestive of moderate chronic small vessel disease in periventricular white matter bilaterally in cerebral hemispheres. CT perfusion study of brain revealed a pattern of small vessel ischemia with bilateral perfusion deficits in inferior frontal lobes, right cerebellum temporoparietal areas. CT angiography did not reveal any large vessel occlusion. MRI revealed chronic bilateral small vessel related ischemic changes but no findings consistent with acute process. A second EEG was obtained demonstrating a severe encephalopathic pattern without epileptiform discharges. Despite extensive work-up, no significant etiology for the persistent encephalopathy could be found. Clinically, the patient's mentation was felt to be most likely a persistent Covid-19 encephalopathy. Family asked about alternative treatment options including experimental therapies in a palliative role. TPE was discussed as an unproven experimental option including the potential risks and possible unproven benefit. The family requested TPE and gave an informed consent. TPE course was begun for a ten-day regimen consisting of five sessions performed every other day. Following the completion of the first TPE session there was significant improvement in the patient's mentation wherein he began following simple one step commands and over subsequent days following multi-step commands consistently. After completion of the TPE course he was noted to consistently visually track staff, follow many verbal commands and eventually began to verbally communicate. Post TPE EEGs revealed significant improvement in the background alpha rhythm with decrease in slow wave activity and absence of epileptiform patterns. Sadly, several days later, he developed severe *Clostridium difficile* infection and recurrent severe respiratory failure. The family elected to pursue hospice care measures upon which the patient subsequently died.

The third case is that of a 62-year-old Bengali male with past medical history significant for chronic obstructive pulmonary disease, hypertension, diabetes, dyslipidemia and schizophrenia. He presented to emergency department with progressive dyspnea, non-productive cough, wheeze, diarrhea, generalized weakness and confusion with unsteady gait. Initial evaluation found the patient to be severely dyspneic, hypoxemic and disoriented with point of care blood glucose of 68 mg/dL that was corrected with dextrose intravenously. He also had acute urinary retention on arrival with 1.2 l in the post void residual scan which was relieved with urinary catheter placement without improvement in his mentation. Laboratory evaluation was notable for mild leukocytosis, mildly elevated serum creatinine (1.46 mg/dL, no previous values to compare) and elevated markers of inflammation. Treatment was begun with Methylprednisolone, Remdesivir, supplemental oxygen and antibiotics. Despite treatment the patient remained profoundly encephalopathic prompting neurologic consultation. During the initial neurologic evaluation, the patient was noted to have clouded sensorium evidenced by unresponsiveness, mute and not making eye contact. Subsequent evaluation was notable for episodic stiffening of limbs and torso without purposeful limb movements. Stat EEG was performed revealing a non-reactive rhythm consistent with alpha coma and without epileptiform patterns. Non contrast CT brain did not reveal evidence of acute intracranial pathology. His clinical status worsened

**Table 1**  
EEG findings in 3 cases and correlation with Plasma Exchange (PLEX)

	Case 1	Case 2	Case 3
Before PLEX	<ul style="list-style-type: none"> <li>● EEG done 5 days before PLEX started</li> <li>● No alpha rhythm, generalized polymorphic theta delta waves, non-reactive to stimuli. No epileptiform patterns seen.</li> <li>● No sedating medications given 12 h prior to EEG.</li> </ul>	<ul style="list-style-type: none"> <li>● EEG done 2 days prior to PLEX started.</li> <li>● Moderately disorganized alpha rhythm 7.5 Hz. Moderate to severe amounts of theta &amp; delta activities.</li> <li>● No epileptiform discharges.</li> <li>● No sedating medications for 12 h prior to EEG.</li> </ul>	<ul style="list-style-type: none"> <li>● EEG done 2 days before PLEX</li> <li>● No alpha rhythm. Alpha coma pattern with 6–7 Hz, nonreactive background rhythm.</li> <li>● No epileptiform discharges seen.</li> <li>● Medications given Zyprexa 2.5 mg three hours before, on Fentanyl drip 10 µg/h &amp; Versed 3 mg/h.</li> </ul>
During PLEX	<ul style="list-style-type: none"> <li>● EEG done 4 h after first PLEX</li> <li>● Severely disorganized alpha rhythm 7.5 Hz reactive to external stimuli. Moderate amounts of theta delta generalized. No epileptiform patterns.</li> <li>● Medication given - Fentanyl 25 µg IVP given 4 h prior to EEG.</li> </ul>	<ul style="list-style-type: none"> <li>● EEG done 5 h after the first PLEX.</li> <li>● Moderately disorganized alpha rhythm. Mild excess polymorphic theta delta activity.</li> <li>● No epileptiform discharges seen.</li> <li>● No sedating medications for 12 h prior to EEG.</li> </ul>	<ul style="list-style-type: none"> <li>● EEG done 1 day after the first PLEX</li> <li>● No alpha rhythm. Large excess polymorphic theta delta activity. Nonreactive to stimuli</li> <li>● No epileptiform discharges seen.</li> <li>● No sedating medication 12 h prior to EEG.</li> </ul>
After PLEX	<ul style="list-style-type: none"> <li>● EEG done 2 days after the last PLEX.</li> <li>● Mildly disorganized alpha rhythm 8 Hz. Mild amounts of theta delta generalized. No epileptiform discharges seen.</li> <li>● No sedating medications 12 h prior to EEG.</li> </ul>	<ul style="list-style-type: none"> <li>● EEG done 1 day after the last PLEX.</li> <li>● Mildly disorganized alpha rhythm 8 Hz. Mild excess polymorphic theta activity. No epileptiform discharges seen.</li> <li>● No sedating medications given for 12 h prior to EEG.</li> </ul>	<ul style="list-style-type: none"> <li>● EEG done 3 h after the last PLEX.</li> <li>● Mildly disorganized alpha rhythm 7.5 Hz. Mild excess polymorphic theta delta activity. No epileptiform discharges seen.</li> <li>● No sedating medications given 12 h prior to EEG.</li> </ul>

approximately one week into admission resulting in endotracheal intubation and mechanical ventilation for several days after which was able to get extubated and freed from mechanical ventilation. A cerebrospinal fluid study including cell counts and bacterial cultures was obtained and the results were unremarkable except for mild protein elevation at 62 mg/dL, mild glucose elevation at 108 mg/dL. Due to his intractable encephalopathy his family expressed interest in pursuing alternative treatment options. At this time TPE was offered with explanation of the risks and benefits and reiteration of the experimental nature of the treatment. The family consented to TPE which was administered in the same fashion as the previous patients. Again, following the first exchange the patient began to demonstrate improved mentation. After completion of the full TPE course he began speaking in brief sentences, recognizing faces and was able to recall the names of his children. EEG studies were obtained similarly to prior patients and noted to show improvement with a true alpha rhythm and a mild encephalopathic pattern. His clinical and mental status improved to the point that he was deemed safe for discharge to a subacute rehabilitation facility.

### 3. Discussion

All three of these patients had persistent severe encephalopathy in the post-acute phase of COVID-19 infection prior to therapeutic plasma exchange. Metabolic derangements, medications and infection were meticulously evaluated and excluded as the etiology. TPE was performed and consisted of 1–1.5 plasma volume exchanges with salinized albumin, performed on alternate days for a total of five treatments. Mental status significantly improved in each of these three cases after TPE, both clinically and on EEG (see Table 1). It is possible that despite adequate peripheral arterial blood pressure the brain suffers hypoperfusion, potentially mediated by a viral or inflammatory vasoactive process at the arteriolar level. Persistent neuronal toxicity from circulating mediators of a post infectious phenomenon that are removed by TPE is also a conceivable possibility. COVID-19 infection may trigger upregulation of inflammatory mediators that persist in many patients for weeks after active infection, possibly contributing to severe suppression of CNS function. In these three reported cases, the resolution of persistent encephalopathy in a few days, with successive plasma exchanges suggests an etiology more likely of a biochemical nature or toxic byproduct in the plasma. Fortunately, weeks after being in a severe encephalopathic state, the toxic effects on the central nervous system were found to be reversible after TPE. In addition to the improvements seen in CNS function, a small randomized trial in patients with severe Covid-19 is reported that found that TPE was associated with higher extubation rates and decreased 14 day and 28-day mortality, providing further support for the potential role of TPE in Covid-19 [14].

Based on these results, a placebo-controlled randomized or case-controlled study for the role of plasma exchange with albumin, in COVID-19 patients with persistent encephalopathy is felt warranted. This may be done with additional monitoring of cerebral perfusion and the measurements of inflammatory mediators to clarify the mechanisms in play. If such objective studies can confirm the findings noted in these three case reports, then the plasma exchange with albumin, could be utilized as an effective treatment in those COVID-19 patients with severe persistent encephalopathy. Plasma exchange may hopefully rescue some of these unfortunate patients from their prolonged comatose states.

### References

- [1] A. Madani Neishaboori, D. Moshrefiaraghi, K. Mohamed Ali, A. Toloui, M. Youseffard, M. Hosseini, Central nervous system complications in COVID-19 patients; a systematic review and meta analysis based on current evidence, *Arch. Acad. Emerg. Med.* 8 (1) (2020), <https://doi.org/10.22037/aaem.v8i1.798>.
- [3] N. Poyiadji, G. Shahin, D. Noujaim, M. Stone, S. Patel, B. Griffith, COVID-19-associated acute hemorrhagic necrotizing encephalopathy: imaging features, *Radiology.* 296 (2) (2020) E119–E120, <https://doi.org/10.1148/radiol.2020201187>.
- [6] Y. Wu, X. Xu, Z. Chen, et al., Nervous system involvement after infection with COVID-19 and other coronaviruses, *Brain Behav. Immun.* 87 (2020) 18–22, <https://doi.org/10.1016/j.bbi.2020.03.031>.
- [7] J. Helms, S. Kremer, H. Merdji, et al., Neurologic features in severe SARS-CoV-2 infection, *N Engl. J. Med.* 382 (23) (2020) 2268–2270, <https://doi.org/10.1056/NEJMc2008597>.
- [8] L. Mao, H. Jin, M. Wang, et al., Neurologic manifestations of hospitalized patients with CoronavirusDisease 2019 in Wuhan, China, *JAMA Neurol.* 77 (6) (2020) 683, <https://doi.org/10.1001/jamaneurol.2020.1127>.
- [10] G. Aghagholi, B. Gallo Marin, N.J. Katchur, F. Chaves-Sell, W.F. Asaad, S. A. Murphy, Neurological involvement in COVID-19 and potential mechanisms: a review, *Neurocrit. Care.* (2020), <https://doi.org/10.1007/s12028-020-01049-4>. Published online July 13.
- [12] C. Iadecola, J. Anrather, H. Kamel, Effects of COVID-19 on the nervous system, *Cell* 183 (1) (2020) 16–27, e1, <https://doi.org/10.1016/j.cell.2020.08.028>.
- [14] F. Khamis, I. Al-Zakwani, S. Al Hashmi, et al., Therapeutic plasma exchange in adults with severe COVID-19 infection, *Int. J. Infect. Dis.* 99 (2020) 214–218, <https://doi.org/10.1016/j.ijid.2020.06.064>.
- [15] J. Matschke, M. Lütgehetmann, C. Hagem, et al., Neuropathology of patients with COVID-19 in Germany: a post-mortem case series, *Lancet Neurol.* 19 (11) (2020) 919–929.

- [16] S.S. Bobati, Therapeutic plasma exchange - an emerging treatment modality in patients with neurologic and non-neurologic diseases, *JCDR* (2017), <https://doi.org/10.7860/JCDR/2017/27073.10480>. Published online.
- [17] Y. Jiang, X. Tian, Y. Gu, F. Li, X. Wang, Application of plasma exchange in steroid-responsive encephalopathy, *Front. Immunol.* 10 (2019) 324, <https://doi.org/10.3389/fimmu.2019.00324>.
- [18] Y.H. Huang, D. Jiang, J.T. Huang, SARS-CoV-2 detected in cerebrospinal fluid by PCR in a case of COVID-19 encephalitis, *Brain Behav. Immun.* 87 (2020) 149, <https://doi.org/10.1016/j.bbi.2020.05.012>.