Plasmapheresis in the Treatment of Refractory Myoclonic Status. A Case Report

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ABSTRACT
A case of myoclonic status treated with plasmapheresis in a patient of 63 years of age who was admitted to a Spanish intensive care unit is reported. The patient showed clinical and radiological evidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection; molecular tests did not verify this.

Keywords: coronavirus, plasmapheresis, neurologic symptoms, myoclonic status

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CASE PRESENTATION

The first symptoms that the patient noticed were anosmia and fever. He presented at the University Hospital 12 October, Madrid, Spain, eight days after the beginning of the symptoms. In the hospital, he developed respiratory failure. Before intubation, "abnormal movements" were observed, so one gram levetiracetam (Altan, Madrid, Spain) was administered intravenously as a single dose.

The patient was intubated and connected to mechanical ventilation admitted to the Intensive Care COVID19 Unit (ICU).

At the time of his admission to the ICU, tests for SARS-CoV2 by qualitative real-time reverse-transcriptase-polymerase-chain-reaction (rRT-PCR) assay could not be performed. Clinic, radiology and blood tests were compatible with severe acute respiratory syndrome SARS-CoV-2 infection.

He received antiviral treatment with 400 mg of lopinavir-ritonavir (Accord Barcelona, Spain) administered twice daily via his enteral feeding tube and 200 mg hydroxychloroquine (Ratiopharm, Madrid, Spain) twice daily also via his enteral feeding tube. Empiric antibiotic treatment was prescribed: 500 mg azithromycin (Ratiopharm, Madrid, Spain) intravenously, once a day and 2 g ceftriaxone (Qilu, Barcelona, Spain) intravenously, twice a day.

At the time of his admission, protective ventilation, high positive end-expiratory pressure was initiated. Day 3 post-admission, after the withdrawal of sedation, a significant intensity of abnormal movements were observed. A neurological examination was undertaken and was compatible with generalized myoclonus.

On day 3 post-admission, the patient was given 2g Valproic acid (Altan, Madrid, Spain) by continuous infusion and 10mg clonazepam (Rivotril®, Roche Farma S.A., Barcelona, SPAIN) intravenously, once daily (Table 1).

On days 5 and 6 post-admission, cranial magnetic resonance imaging (MRI), and cerebrospinal fluid analysis were performed, revealing no abnormalities. Serial electroencephalography tests on day 6 and 9 post-admission were performed with no abnormal cortical activity.

The patient was discharged to conventional hospitalization on day 10 post-admission.

During his stay in the neurology ward, myoclonus worsened, preventing the patient from moving, speaking or swallowing.

Keeping in mind a possible immune-mediated reaction, immunotherapy was started with 1 g Methylprednisolone (Normon 40mg, Madrid, Spain) given intravenously once a day.

A partial clinical response was observed but, on day 12 post-admission to the ICU, the patient had persistent "myoclonic storm", stiffness and a lack of response to the treatment administered so far, as well rescue-ad-
ministered benzodiazepines, 3 mg bromazepam (Normon capsula, Madrid, Spain) which had been administered via his enteral feeding tube and 20 mg diazepam intravenously.

Due to continuous muscle activity, including the oropharyngeal musculature, low oxygen saturation and intermittent cyanosis, on day 12 post-admission, the patient was readmitted to the ICU for sedation and re-intubated.

High doses of sedatives and four antiepileptic drugs were prescribed to control the myoclonic status (Table 1). Despite this, his evolution was not favourable with no other identifiable cause except the possibility of an inflammatory origin.

On the first day of readmission to the ICU (day 12 post-admission), a decision was made to perform plasmapheresis. A high flow catheter was placed in the patient's groin and connected to an extracorporeal purification machine.

A polytetrafluoroethylene (PTFE) membrane filter was used with a dosage of 40 mL/kg. A total of five sessions (once a day) of plasmapheresis with albumin 5% replacement were performed. No adverse events were noticed during the treatment.

On Day 15 post-admission to the ICU, all sedation was withdrawn. There was an improvement of the neurological status, and the patient was discharged once more to conventional hospitalization.

At the time of writing this case report, the patient continues to exhibit less intense myoclonic movements. He can eat and drink unaided and makes attempts at writing.

**Discussion**

A literature review indicated that several papers had been published regarding neurological involvement in SARS-CoV-2 infection [1,2] but only one refers to myoclonic status [3].

The aetiology of myoclonic status remains unknown. The aetiologies considered in the patient's differential diagnosis were epilepsy, toxic or drug-related causes, metabolic-related, infectious disease, and inflammatory, dysimmune neuropathies, stroke, or functional causes. Each of these is now discussed.

A paradoxical reaction to benzodiazepines would have responded to discontinuation of the drug [4] and propofol infusion.

Regarding opioids, myoclonus has been mostly described in patients on chronic treatment. The patient received a high dose of morphine during the acute phase of the disease, as intubation-associated analgesia.

### Table 1. Treatment timeline

| Treatment       | Time (days since ICU admission) |
|-----------------|---------------------------------|
| Levetiracetam   | 1a, 2, 3b, 4, 5, 6, 7, 8, 9, 10c, 11, 12d, 13, 14, 15, 16, 17, 18, 19e, 20f |
| Diazepam        |                                 |
| Propofol        |                                 |
| Midazolam       |                                 |
| Cisatracurium   |                                 |
| Valproic acid   |                                 |
| Corticosteroids |                                 |
| Clonazepam      |                                 |
| Perampanel      |                                 |
| Plasma exchange |                                 |

| Treatment       | Time (days since ICU admission) |
|-----------------|---------------------------------|
| Levetiracetam   | 1000 mg/24h                     |
| Levetiracetam   | 3000 mg/24h                     |
| Diazepam        | 30 mg/24h                       |
| Diazepam        | 7.5 Mg/24h                      |
| Propofol        | 4 mg/kg/h                       |
| Propofol        | 1.4 Mg/kg/h                     |
| Midazolam       | 7.5 Mg/24h                      |
| Midazolam       | 0.16 Mg/kg/h                    |
| Cisatracurium   | 0.18 Mg/kg/h                    |
| Valproic acid   | 1200 mg/24h                     |
| Valproic acid   | 400 mg/24h                      |
| Valproic acid   | 2000 mg/24h                     |
| Metilprednisolone| 250 mg/24h                     |
| Metilprednisolone| 1000 mg/24h                   |
| Clonazepam      | 3 mg/24h                        |
| Clonazepam      | 6 mg/24h                        |
| Clonazepam      | 2 mg/24h                        |
| Perampanel      | 6 mg/24h                        |
| Perampanel      | 8 mg/24h                        |
| Plasma exchange |                                |
Metabolic-related. Blood urea nitrogen, the partial pressure of carbon dioxide, ammonia, liver enzymes, calcium, magnesium, and potassium, were normal. Lance-Adams syndrome [5] or post-hypoxic myoclonus is a rare complication described after a cardiorespiratory arrest. The patient did not have significant hypoxia for an extended period, and both intubations occurred without relevant desaturation. Thyroid hormones were slightly altered with low T3 syndrome and moderately elevated Thyroid-stimulating Hormone (TSH) (10 mUI/L). Moreover, anti-thyroglobulin antibodies were detected, but the administration of Levo-thyroxine did not change the intensity of symptoms.

Infectious disease. Cerebrospinal fluid analysis and cytology examination were normal. Viral polymerase-chain-reaction tests had a negative result for herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus (VZV), human cytomegalovirus (CMV), Epstein-Barr virus and human herpesvirus type 6. Bacterial and fungi tests were negative. Viral serologies were negative. More rare etiologies like Whipple disease or Creutzfeldt-Jakob disease have different onset of symptoms.

Inflammatory or dysimmune disease. Progressive encephalomyelitis with rigidity and myoclonus (PERM) or “stiff-person plus disease” cases have been reported as a neurological manifestation of cytokine release syndrome (CRS) in CAR-T cell therapy, more accurately in the recently named “Immune effector cell-associated neurotoxicity” syndrome (ICANS) [6,7]. Similar pathogenesis and treatment targeted to key cytokines have been described in COVID19 disease [8]. Other aetiologies considered were autoimmune and paraneoplastic encephalitis. The patient did not have any clinical or radiological findings compatible with tumoral disease. A test to identify anti-glutamic acid decarboxylase (GAD) antibodies, anti-neuronal antibodies and Anti-N-methyl-d-aspartate (NMDA) antibodies was performed and was negative. Acute disseminated encephalomyelitis (ADEM), a disease in the spectrum of multiple sclerosis in which myoclonus has been described [9], but this would have been visible on MRI. Finally, spinal myelitis was highly improbable. The patient suffered exclusively diffuse motor affection with a facial predominance (this is not concordant with spinal myelitis topography). No motor or sensory spinal level was found in the clinical exam. Neuromyelitis Optica primarily affects the eye nerves, and it is rarely associated with myoclonus. As spinal cord involvement is extensive in this condition, it would have probably shown T2 hyperintensity in the cerebral MRI study’s high cervical cuts.

Stroke. MRI and computerized tomography (C.T.) scan imaging to rule out this diagnosis. Remarkably, a different patient from our hospital myoclonus series with persistent positive PCR of SARS-CoV2 suffered an ischemic stroke of the cerebellum and midbrain. No thrombi or emboli were found in contrast-enhanced computed tomography. The patient did not suffer from cardiac arrhythmias, and transthoracic echocardiography was normal. Similar cases have been reported in the literature [2]

Functional. This was considered a low probability given the severity of the disease.

We hypothesize that myoclonus could be another symptom of the advanced hyperimmune phase[10] in patients with coronavirus infection, especially those who referred to anosmia in the initial disease pattern (potential neuroaxis involvement). Therefore, plasmapheresis therapy could be considered part of this syndrome’s therapeutic arsenal, whose consequences are functional incapacity and potential vital compromise if the symptoms are severe.

**CONCLUSION**

After plasmapheresis, the patient’s clinical evolution was satisfactory, with progressive improvement of the neurological symptoms and partial recovery of his functional status. However, the symptoms’ resolution may not necessarily be due to the treatment itself but to the disease’s natural evolution.

A greater understanding of the pathophysiology is needed to help manage these patients.

**LIST OF ABBREVIATIONS**

ADEM: acute disseminated encephalomyelitis
CMV: cytomegalovirus
CT: computerized tomography
GAD: glutamic acid decarboxylase
HSV-1: Herpes simplex virus type 1
HSV-2: Herpes simplex virus type 1
ICU: Intensive Care Unit (ICU)
MRI: magnetic resonance imaging
NMDA: N-methyl-d-aspartate
PEEP: positive end-expiratory pressure
PTFE: polytetrafluoroethylene
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
RRT-PCR: reverse-transcriptase-polymerase-chain-reaction
TSH: Thyroid-stimulating Hormone
VZV: varicella-zoster virus

**CONFLICT OF INTEREST**

None to declare.

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