

# Presumed Recent-Onset Refractory Status Epilepticus (NORSE) Post-COVID-19 Plasmapheresis and Itolizumab: Case Report

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**Abstract:** Introduction: Recent-onset refractory status epilepticus (NORSE) is a neurological emergency that leads to morbidity and mortality, with rapid evolution, poor prognosis; uncommon entity in patients without active epilepsy, without clear acute or active structural, toxic or metabolic cause; and not associated with any etiology. The management of this disease is not clearly defined and has been poorly described so far in the literature. Cases of NORSE associated with COVID-19 illness have been reported. However, the frequency related to SARS-CoV-2 infection is unknown, it is a novel case in our environment. Objective: to evaluate the effectiveness of therapeutic plasmapheresis and Itolizumab as coadjuvant therapy in the treatment of this entity. Methodology: Our research reports a case of a young patient with a history of previous health, admitted to the intensive care unit of the Arnaldo Milián Castro Hospital, in February of this year, due to repetitive seizures that are difficult to control, with a precedent of respiratory manifestations. acute (runny nose) the week before; to the course of the NORSE, it was direct contact of a confirmed case to COVID-19; Due to the fact that there are pathogenic substances in the plasma that contribute to the disease process, plasmapheresis and treatment with Itolizumab are proposed to support the therapy of this entity. Conclusions: Therapeutic plasmapheresis and itolizumab constituted a correct approach in the treatment of this clinical condition associated with presumptive post-COVID-19.

**Keywords:** Post COVID-19, Refractory Status Epilepticus (NORSE), Therapeutic Plasmapheresis, Itolizumab

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## 1. Introduction

Terms related to Epilepsy have recently appeared in the literature, linked to the presence of Status Epilepticus as: "a condition resulting from the failure of the mechanisms responsible for the termination of epileptic seizures or the initiation of mechanisms that lead to epileptic seizures abnormally prolonged, which can have long-term consequences depending on the type and duration of the crises". Therapies to interrupt status epilepticus and with a very dark and unclear prognosis, have led to extensive study in the last almost 15 years of this century. It is a rare disorder with 50% unknown cause [1]. Common causes seen in the

intensive care unit with this disease, (including stroke, infection, and subtherapeutic antiepileptic drug levels in patients with epilepsy) A less common cause of status epilepticus is often identified as autoimmune status epilepticus (ASE), caused by autoantibodies that cause rapidly progressive encephalopathy, abnormal movements, recurrent seizures, and often psychiatric symptoms. Causal antibodies such as NMDA, LGI1, GABABR, GABAAR and GAD have been identified by different laboratory techniques [2]. Recent-onset status epilepticus (NORSE) is a clinical syndrome characterized by refractory status epilepticus in a patient with no history of previous neurological disease. It constitutes one of the neurological emergencies that is

difficult to diagnose, and its importance lies in the fact that a percentage of them are refractory, resulting in high morbidity and mortality, which requires rapid identification and timely treatment. Among the most frequent causes are immune-mediated entities, mainly autoimmune encephalitis due to anti-NMDA receptor antibodies. Some authors suggest that early immunotherapy could be beneficial, even when a definite autoimmune etiology has not been identified. There are few records of this entity in our setting. The proposed consensus definitions are as follows: NORSE is a clinical presentation, not a specific diagnosis, in a patient without pre-existing active epilepsy or other relevant neurological disorder, with new onset of refractory status epilepticus without a clear acute or active pattern, toxic or metabolic. FIRES is a subcategory of NORSE, applicable for all ages, requires a previous febrile infection starting between 2 weeks and 24 hours before the onset of refractory status epilepticus. The COVID-19 pandemic represents one of the greatest emergencies that humanity has had to face in the last century; SARS-CoV-2 infection may be associated with acute neurological manifestations [3]. Although knowledge of acute central nervous system (CNS) comorbidities is increasing, little is known about the possible neurological sequelae of infection. Given the pathophysiology proposed for NORSE, based on a neuroinflammatory mechanism, different immunotherapies have been used as part of its treatment; Other additional ones that have been tested in NORSE show a sequential algorithm according to the alternatives: as the first line of treatment, immunotherapy consists of intravenous corticosteroids, intravenous immunoglobulins (Ig-IV) and plasmapheresis; immunosuppressive drugs such as cyclophosphamide, tacrolimus, and others are also described as second-line treatment; as well as rituximab, which is a chimeric anti-CD20 monoclonal antibody, IL-6 receptor inhibitor tocilizumab, among others, reporting data on the clinical benefit and safety of these treatments [4-6]. This case report is novel due to the characteristics described in the case of a 22-year-old female patient with a previous health history, admitted to the intensive care unit (ICU) of the Arnaldo Milián Castro Hospital, with new refractory status epilepticus appearance (NORSE), which weeks before the data is collected that it was a contact of a confirmed case of COVID-19, which makes it suspicious of a presumed case of post-COVID-19. Due to previous bibliographical consultations and studies of similar cases, the medical team considered indicating therapeutic plasmapheresis together with Itolizumab, a humanized monoclonal antibody CD6, of national production; The patient showed rapid and significant clinical improvement after treatment and was discharged with normal cognition and minor ataxia, which improves with physical rehabilitation therapy [7, 8].

## 2. Method

A novel case of observational study of a 22-year-old female patient with previous health history, admitted from

February to March of the current year, in the intensive care unit of the Arnaldo Milián Castro Hospital in serious condition, with recent-onset, repeated, difficult-to-control seizures; where she was diagnosed with NORSE-FIRES, being her clinical evolution towards the critical state, taking into account previous studies and the inclusion criteria of therapeutic plasmapheresis together with monoclonal antibodies in the treatment of patients with NORSE, achieving satisfactory results, is that It is indicated by the medical assistance team to use this combination of therapy in this case, also presumptive post-COVID-19, the information analyzed was collected in the clinical history of the evolution and the laboratory parameters of the patient, also documenting the medications that are used for this entity, the frequency of therapeutic plasmapheresis sessions and the doses of Itolizumab were taken into account. A. Itolizumab Cuban-produced anti-CD6 humanized monoclonal antibody: Indicated for the treatment of confirmed SARS-CoV-2 adult patients with critical, severe or moderate disease with a high risk of worsening. Authorized for use by the Cuban Medical Equipment and Devices Regulatory Center by its acronym in Spanish (CECMED). Patients must be hospitalized in the conventional ward or in intensive care units and have suspected cytokine release syndrome. It should not be used in patients receiving other biological medicinal products. B. Therapeutic plasmapheresis Therapeutic plasmapheresis, also known as therapeutic plasma exchange, is defined as a therapeutic technique or procedure of extracorporeal blood purification, which consists of the extraction of a certain volume of plasma (from 2 to 5 liters), whose purpose is to eliminate or remove large molecular weight particles, pathogens or to reduce the rate of circulating immune complexes or other components present in the plasma that intervene in the pathological immune response and that are considered responsible for a disease or its clinical manifestations. Selective plasma removal should be replaced by crystalloid/colloidal solution or fresh frozen plasma. In our research we use centrifuge technology. The Nigale plasma apheresis system of the automated separating centrifugal machine was used, which uses a two-stage continuous flow separation chamber. Plasmapheresis was performed on the patient through the antecubital route in the upper limbs. The procedures were programmed to remove a volume of plasma per procedure (approximately 40 ml/kg of patient weight), which was replaced with crystalloid/colloid solutions; fresh frozen plasma was not used.

## 3. Results

Cases of NORSE have recently been reported in patients infected with the SARS-CoV-2 coronavirus, both symptomatic and asymptomatic, and it is suggested that it may be caused by the immune response with compromise of the Central Nervous System (CNS) [9, 1]. In the presumptive post-COVID-19 case presented, although the results were

negative for TR-PCR in the patient, the data is collected that weeks before the convulsive state she was direct contact of a confirmed case with COVID-19 [10, 11]. In the intensive care unit where she was admitted due to her convulsive state of recent onset and difficult to control; They began with the appropriate treatment for this type of entity with benzodiazepines, phenobarbital, Ketamine, Propofol, antibiotic therapy, dexamethasone, oxygen therapy (invasive mechanical ventilation), among others [12, 13]. The aggravation of the patient in the clinical course due to multiple complications brings with it after the ninth day of her admission that the medical group decided to start the first session of therapeutic plasmapheresis, 24 hours after this procedure, in the results of the electroencephalogram, a flattening of paroxysmal curves; Therapeutic plasmapheresis sessions continued at 48-hour intervals, replacing liquid with colloidal solutions. In addition, calcium gluconate was taken into account preventively to avoid hypocalcemia due to the use of sodium citrate anticoagulant and 0.80g dextrose [14, 10]. After the third session of plasmapheresis, it was indicated to include Itolizumab as a treatment, appreciating clinical improvement in the patient 24 hours after this combination, and it was decided by the medical team to reduce sedation; No adverse effects were described with the use of plasmapheresis or Itolizumab. A total of five sessions of plasmapheresis procedures were performed, observing a notable improvement in clinical status and laboratory parameters, thus achieving recovery three days after the last plasmapheresis session and itolizumab [15]. The patient's stay in the intensive care unit was 21 days and she was transferred to the neurology service of the same hospital; where she is discharged on the fifth day of stay in this service.

## 4. Conclusions

NORSE is a clinical presentation that, associated with COVID-19, can constitute a real diagnostic challenge in medical sciences. Its timely treatment improves the prognosis of this entity to minimize the incidence of disability and mortality. Therapeutic plasmapheresis and itolizumab constituted a correct approach in the treatment of this clinical condition associated with presumptive post-COVID-19.

## Conflict of Interest Statement

All authors have no potential conflicts of interest.

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