LUMEN ET VIRTUS

Neurological complications associated with COVID-19: Systematic review of evidence on manifestations, complications, and pathological mechanisms

https://doi.org/10.56238/levv15n40-028

Julia Garcia Stela[1], Laura Giacometti Bittar[2], Fabrício Francisco da Silva Júnior[3], Pedro Paulo Frias[4], Guilherme Sberni Rodrigues, Ana Clara Junqueira Tedeschi, Isadora de Pádua Beretta González[5], Giovanna Cristina Ferreira dos Santos[6], Maria Julia da Costa[7], Beatriz Pantano dos Santos[8], Ruan Júnior Lopes Bicalho[9].

ABSTRACT

Objective: To analyze the complex synergistic interaction between Covid-19 and the neurological manifestations caused by the infection, exploring the clinical, epidemiological and pathophysiological implications. It also seeks to evaluate the diagnostic challenges faced by patients and discuss public health strategies. Methodology: It is a systematic review focused on understanding the main aspects of Covid-19 co-infection and neurological symptoms. The research was guided by the question: 'What are the biological and immunological mechanisms underlying the interaction between SARS-CoV-2 and the development of neurological complications and how do they affect susceptibility, disease progression and the clinical manifestations of patients?' To find answers, we searched the PubMed database using four descriptors combined with the Boolean term "AND": Guillain-Barre Syndrome, COVID-19, SARS-CoV-2, and COVID-19 Vaccines. This resulted in 562 articles. 19 articles were selected for analysis. Results: It is evident that the neurological involvement associated with COVID-19 covers a wide variety of manifestations, from milder symptoms, such as headache and smell and taste disorders, to more severe complications, such as encephalopathy, encephalitis, seizures, and strokes. These manifestations appear to be influenced by mechanisms such as systemic inflammation, hypoxia, direct viral invasion of the central nervous system (CNS), and exaggerated immune responses, which can result in irreversible damage to nervous tissue. Conclusion: The review highlights the importance of early diagnosis and close clinical monitoring to improve outcomes.

Keywords: SARS-CoV-2, Neurological complications, Clinical manifestations.

[1] Universidade de Franca (UNIFRAN), Franca - SP
[2] Universidade de Franca (UNIFRAN), Franca - SP
[3] Universidade de Franca (UNIFRAN), Franca - SP
[4] Universidade de Franca (UNIFRAN), Franca - SP
[5] Centro Universitário Municipal de Franca (FACEF), Franca – SP
[6] Federal University of Triângulo Mineiro (UFTM), Uberaba – MG
[7] Federal University of Triângulo Mineiro (UFTM), Uberaba – MG
[8] Federal University of Triângulo Mineiro (UFTM), Uberaba – MG
[9] Physician from the Faculty of Medicine of Marília (FAMEMA) - Marília - SP, General Practitioner and gastroenterologist

INTRODUCTION

In December 2019, an outbreak of pneumonia of viral origin began in the city of Wuhan, China, linked to a new coronavirus, initially called the Wuhan virus or the new coronavirus in 2019. What started as a local epidemic has evolved into a global pandemic with severe consequences. In February 2020, an official nomenclature was established for the new virus: 'coronavirus (CoV) type 2 associated with severe acute respiratory syndrome (SARS)' (SARS-CoV-2), due to the disease it causes, COVID-19. The World Health Organization declared the epidemic a public health emergency of international concern on January 30, 2020, and thereafter as a worldwide pandemic. As of May 3, 2020, the pandemic had affected more than 200 countries, with 3,349,786 confirmed cases of COVID-19, including 238,628 deaths as of March 11, 2020, the World Health Organization (WHO) has recognized the COVID-19 outbreak as a pandemic linked to severe acute respiratory syndrome (CAROD-ARTAL, 2020) (RODRÍGUEZ et al., 2022) (WANG et al., 2020).

The coronavirus is a virus encased in a capsule and has one of the largest genomes among positive-sense single-stranded RNA viruses, ranging between 26 and 32 kilobases. The term 'coronavirus' derives from its crown-shaped appearance, visible through electron microscopy, due to the presence of glycoproteins in a spike around its membrane. The coronavirus belongs to the subfamily Ortocoronavirinae, of the family Coronaviridae, order Nidovirales (CAROD-ARTAL, 2020). To date, six coronavirus families have been identified, and the new SARS-CoV-2 represents a significant threat to human health. Four of these coronaviruses are associated with mild seasonal respiratory diseases, which correspond to 15-30% of upper respiratory tract infections with high global prevalence (RODRÍGUEZ et al., 2022).

There is growing evidence of neurological complications detected in patients infected with SARS-CoV-2. Viral neuroinvasion can occur through several routes, such as entry through the olfactory nerve, transsynaptic transfer between infected neurons, leukocyte migration across the blood-brain barrier (BBB), or infection of the vascular endothelium (JHA et al., 2021).

Nervous system impairment may be due to a direct action of the virus on nervous tissue and/or an indirect action through the activation of immune mechanisms. While the first action can occur during the acute phase of the disease, the second can manifest days, weeks, or even months after this phase. Many viral infections can impair the structure and function of the nervous system, resulting in conditions such as encephalitis, toxic encephalopathy, and post-infectious demyelinating diseases. Coronaviruses can invade

nerve tissues involving macrophages, microglia, or astrocytes with immune function, and cause nerve damage through direct infection (circulatory and neuronal route), hypoxia, immune injury, attack on ACE2 enzymes, and other mechanisms (BEGHI et al., 2020).

The clinical spectrum of severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection is extensive, ranging from asymptomatic infections, mild upper respiratory tract illness, to severe pneumonia with respiratory failure, which sometimes leads to death. The most common neurological complaints in COVID-19 include anosmia, ageusia, and headache, as well as other manifestations such as fever, fatigue, myalgia, dry cough, and diarrhea. Cases of coma, seizures, stroke, encephalopathy, and impaired consciousness were also recorded in 2020. The identification and understanding of the set of neurological diseases associated with COVID-19 can result in better clinical outcomes and more efficient therapeutic protocols (JHA et al., 2021) (ROMOLI et al., 2020).

The objective of this work is to examine the complex synergistic interaction between SARS-CoV-2 infection and the emergence of neurological manifestations, exploring the clinical and epidemiological implications of this co-infection. It is also intended to evaluate the diagnostic and therapeutic challenges faced by co-infected patients and to discuss public health strategies that have contributed to the improvement of clinical outcomes.

METHODS

This is a systematic review that seeks to understand the main aspects of the relationship between SARS-CoV-2 infection and associated neurological manifestations, as well as to demonstrate the pathophysiological mechanisms and clinical picture, aiming to ensure a greater clinical elucidation of these pathologies. For the development of this research, a guiding question was elaborated through the PVO (population, variable and objective) strategy: 'What are the biological and immunological mechanisms underlying the interaction between SARS-CoV-2 and the development of neurological manifestations and how do they affect susceptibility, disease progression and clinical manifestations of patients?'

The searches were carried out through searches in the PubMed Central (PMC) databases. Four descriptors were used in combination with the Boolean term "AND": Guillain-Barre Syndrome, COVID-19, SARS-CoV-2, and COVID-19 Vaccines. The search strategy used in the PMC database was: (Guillain-Barre Syndrome) AND (COVID-19), (Guillain-Barre Syndrome) AND (SARS-CoV-2) and (Guillain-Barre Syndrome) AND (COVID-19 Vaccines). From this search, 562 articles were found, which were subsequently submitted to the selection criteria. The inclusion criteria were: articles in English,

Portuguese and Spanish; published in the period from 2019 to 2024 and that addressed the themes proposed for this research, in addition, review, observational and experimental studies, made available in full. The exclusion criteria were: duplicate articles, available in the form of abstracts, that did not directly address the proposal studied and that did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 562 articles were found. After applying the inclusion and exclusion criteria, 31 articles were selected from the PubMed database, and a total of 19 studies were used to compose the collection.

DISCUSSION

According to the classifications described in some reports, out of 4.8 million identified cases of COVID-19, central nervous system (CNS) and peripheral nervous system (PNS) complications were observed in 1,805-9,671 and 2,407-7,737 patients, respectively. The brain, as it performs a vital function, is protected from lesions of various origins by different mechanisms. The skull is the main protection against physical injury and is reinforced to protect brain tissue. The defense against pathogens and harmful chemical agents is mainly done by the blood-brain barrier (BBB), which is composed of endothelial cells that selectively regulate the passage of substances present in the bloodstream to the CNS, such as antibodies, the complement system, and coagulation factors. To access such a well-protected organ, coronavirus 2 has different strategies to invade the CNS, bypassing the BBB (HOSSEINI; NADJAFI; ASHTARY, 2021) (MENDONÇA FILHO et al., 2023).

Nervous system impairment may occur due to a direct action of these viruses on nervous tissue and/or an indirect action through the activation of immune-mediated mechanisms. Although the first action can be observed during the acute phase of the disease, the second can only be noticed after days, weeks, or even months after the acute phase. Many viral infections can compromise the structure and function of the nervous system, manifesting as encephalitis, toxic encephalopathy, and post-infectious demyelinating disease. Coronaviruses can invade nervous tissues using macrophages, microglia, or astrocytes with immune function, causing nerve damage through direct infection pathways (circulatory and neuronal), hypoxia, immune injury, attack on ACE2 enzymes, and other mechanisms (BEGHI et al., 2020).

Invasion occurs by retrograde axonal transport of the olfactory system, either through the BBB or by being carried by infected immune cells. The SARS-CoV-2 spike protein binds to angiotensin-converting enzyme-2 (ACE2) for internalization, although other surface

proteins may act as a cofactor. SARS-CoV-2 uses ACE 2 and serine protease 2 transmembranes (TMPRSS2) as receptors to bind to cells and infect them. ACE2, a surface protein present in many cell types, is highly expressed in the choroid plexus and found in neurons, astrocytes, oligodendrocytes, and endothelial cells. Direct invasion of the virus can result in cell death or inflammatory infiltration of neutrophils and macrophages activated by invading endothelial cells (endotheliitis), which leads to endothelial cell damage and thromboinflammation (VALDERAS et al., 2022) (ARIÑO et al., 2022).

SARS-CoV-2 can trigger a hyperinflammatory state, mainly through cytokine storm and macrophage activation. This immune dysregulation is associated with high levels of inflammatory biomarkers such as C-reactive protein, erythrocyte sedimentation rate, fibrinogen, D-dimer, ferritin, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and procalcitonin. This cytokine release syndrome may contribute to many of the clinical and laboratory findings reported in severe COVID-19: increased cytopenias, coagulopathy, hyperferritinemia, and other acute phase reactants (e.g., CRP, D-dimer), endothelial damage, and vascular permeability. In the brain, these cytokines can compromise BBB and trigger local amplification, eliciting an innate immune response in resident cells that express toll-like receptors (HOSSEINI et. al., 2021) (VALDERAS et al., 2022) (ARIÑO et al., 2022).

SARS-CoV-2 infection is a potent trigger of this immune hyperactivation, with high levels of cytokines being detected in patients with COVID-19, both in serum and CSF, with worse prognosis and multiple organ failure. In particular, IL-6 may be a promising biomarker for severity and therapeutic decision-making, as antagonizing IL-6 directly or via the JAK-STAT pathway has demonstrated a better prognosis in hospitalized COVID-19 patients with hypoxia and systemic inflammation. This cytokine storm has some specific characteristics of COVID-19, such as being often accompanied by lymphopenia, in contrast to other diseases (ARIÑO et al., 2022).

By invading the CNS, regardless of the access route, SARS-CoV-2 causes the activation of microglia. It is relevant to mention that activated glial cells are markers of neuropathologies, brain lesions, and neuroinflammation. While microglial cells are not the only cell type responsible for triggering inflammatory responses in the brain, systemic immune cells can also induce neuroinflammation due to the release of pro-inflammatory substances. They respond quickly to environmental changes. When these cells are activated, in addition to phagocytosing damaged cells, they secrete quinolinic acid, interleukins, complement system proteins, and TNF-α. In this context, the increase in quinolinic acid, an agonist of the N-methyl-D-aspartate (NMDA) receptor, leads to

neurotoxicity and can affect memory, learning, neuroplasticity, and cause hallucinations (MENDONÇA FILHO et al., 2023).

When a virus proliferates in lung tissue cells, it causes diffuse alveolar and interstitial inflammatory exudation, edema, and formation of hyaline membranes. This, in turn, results in disturbances in alveolar gas exchange, generating hypoxia in the CNS, increasing anaerobic metabolism in the mitochondria of brain cells. The accumulation of acid can cause cerebral vasodilation, edema of brain cells, interstitial swelling, obstruction of cerebral blood flow and even headache due to ischemia and congestion. If hypoxia continues, cerebral edema and cerebral circulation disorder may worsen significantly. In intracranial hypertension, brain function gradually deteriorates, and drowsiness, bulbar conjunctival edema, and even coma may be observed (WU et al., 2020).

COVID-19 primarily causes a severe and fatal respiratory syndrome, with some specific neurological symptoms in the CNS, including dizziness, neck stiffness, headache, acute impairment of consciousness, acute cerebrovascular disease, ataxia, hyposmia, hypogeusia, neuralgias and seizures (HOSSEINI; NADJAFI; ASHTARY, 2021). In a retrospective study of 214 patients infected with COVID-19 in a hospital in Wuhan, 36.4% had some type of neurological manifestation, which was classified as CNS (24.8%), peripheral (10.7%), and musculoskeletal (10.7%) affectation. The most common neurological symptoms were dizziness (36 cases), headache (28 cases), hypogeusia (12 cases), and hyposmia (5 cases). Neurological symptoms were more frequent in severe COVID-19 patients (45.5% versus 30%) (CAROD-ARTAL, 2020)

The most common symptom of the central nervous system (CNS) is headache, with prevalence rates ranging from 6.5% to 23% and an average of 8% in several studies. In a study conducted in Wuhan, 8% of patients mentioned headache as a symptom, while a survey from Zhejiang identified that 34% of patients had headache. In another French study, 82% of COVID-19 cases reported headaches as a manifestation. A recent study with 130 patients hospitalized with COVID-19 found that 35% had severe headaches, with a predominance in the frontal region and oppressive character. The investigation also revealed that 62% of these patients experienced headaches in the first 24 hours after contracting the disease. Almost half of the people had tension-type headaches. Generally, migraines, tension headaches, and acute headaches associated with flu-like conditions prevail in the first days of the disease. Headaches caused by hypoxia and systemic inflammation, resulting from a cytokine storm, may occur in later stages. In cases of venous sinus thrombosis and meningitis related to COVID-19, headaches can be premonitory signs (MAGAR et al., 2022).

One of the most evident manifestations reported in patients with COVID-19 is the loss or alteration of smell (anosmia or hyposmia) and/or taste (dysgeusia). Anosmia and, secondarily, taste changes appear to be very prevalent among people with COVID-19, even without nasal symptoms, and can come on suddenly. The prevalence of olfactory and gustatory dysfunction was analyzed in a registry of 12 European hospitals. A total of 417 patients with COVID-19 participated in the study, ranging from moderate to severe. Participants answered questions about changes in taste and smell based on a nutritional and health examination consultation and the short version of the olfactory disorders questionnaire (CAROD-ARTAL, 2020) (KORALNIK; TYLER, 2020).

Both anosmia and ageusia can occur in isolation (idiopathic) or in association with structural damage to the nervous system. Several neurological conditions can include olfactory impairment, such as head trauma, multiple sclerosis, Parkinson's disease, and Alzheimer's. More often, between 11% and 40% of patients with upper respiratory tract infection, common cold, or flu may present with anosmia or hyposmia. Although the pathophysiological mechanisms related to anosmia and ageusia in SARS-CoV-2 are not fully understood, studies in mice have shown that the virus can penetrate through the olfactory bulb. In addition, oral mucosal cells have ACE2 receptors, which are used by the virus to enter cells. Dysfunction of the dopaminergic pathway is also suspected to be involved in anosmia in SARS-CoV-2-infected patients. Finally, SARS-CoV-2 can infect the lining of the nasal cavity, causing localized inflammation (MUNHOZ et al., 2020).

A study of 31 patients suggested that disturbances in taste occurred in 81% of COVID-19 cases (46% anosmia, 29% hyposmia, and 6% dysosmia) and taste dysfunction in 94% (ageusia 45%, hypogeusia 23%, and dysgeusia 26%). The mean duration of changes in smell and taste was 3.1 days (KORALNIK; TYLER, 2020). It has been suggested that these dysfunctions may indicate neuroinvasion and offer a pathway to the cardiorespiratory centers in the spinal cord, from the oropharynx and nasopharynx. These hypotheses are based on studies carried out on transgenic mice infected with SARS-CoV, which express the human receptor of the virus (ACE2). Currently, there is no evidence to prove this route of entry in humans (JHA et al., 2021).

Encephalopathy is an umbrella term that describes brain disease, damage, or malfunction with a wide range of symptoms, such as memory loss, personality changes, dementia, seizures, coma, or even death (HOSSEINI; NADJAFI; ASHTARY, 2021). The risk of developing an altered mental state associated with COVID-19 is higher in older people or people with pre-existing cognitive impairment, as well as those with vascular risk factors (hypertension) and comorbidities. Patients with prior neurological injury and acute

respiratory symptoms are at increased risk of developing encephalopathy as an early manifestation of COVID-19. Encephalopathy was independently associated with a higher mortality rate in the first 30 days after hospitalization and an increased incidence of neuropsychiatric disorders in the six months after COVID-19 diagnosis (CAROD-ARTAL, 2020) (ARIÑO et al., 2022)

Encephalopathy is manifested by an altered mental state, sometimes accompanied by physical symptoms, such as difficulty in coordinating limb movements. Generally speaking, encephalopathy is not an isolated disease, but rather an umbrella term for injuries or conditions that affect mental status. Encephalopathy can arise after withdrawal of mechanical ventilation, possibly due to the prolonged effects of sedation or ventilation, and usually resolves within a short period. The infection can reach the brain through inflammatory responses, leading to encephalopathy; therefore, encephalitis should be considered when there is CSF pleocytosis, imaging changes, focal seizures, or histological findings that indicate brain inflammation. Encephalopathy can persist for weeks or even months, and is possibly aggravated by bacterial infections during ventilation. In addition, encephalopathy was observed in 16 (7%) of 214 COVID-19 patients in China and in 40 (69%) of 58 ICU patients in France (HOSSEINI; NADJAFI; ASHTARY, 2021).

Encephalitis refers to inflammation in the brain parenchyma caused by pathogens, including neuronal lesions and damage to nerve tissue. It is characterized by a rapid onset and common symptoms such as headache, fever (especially high fever), vomiting, seizures, and changes in consciousness. Encephalitis is an encephalopathy marked by brain inflammation in response to some underlying insult. This condition can be divided into three types: infectious encephalitis, caused by the direct invasion of the brain by a microorganism; post-infectious encephalitis, caused by the host's immune response after an infection; and autoimmune encephalitis, which is not directly related to an infection. As already mentioned, COVID-19 can reach the brain directly through the virus or the immune response. During the ongoing pneumonia epidemic, medical staff at Ditan Hospital in Beijing detected SARS-CoV-2 in the cerebrospinal fluid of COVID-19 patients through genomic sequencing, clinically confirming viral encephalitis. This provided a solid foundation for CoV as a cause of encephalitis. (MENDONÇA FILHO et al., 2023) (WU et al., 2020).

About 9% of people who have contracted COVID-19, especially those in serious condition, may have impairments in the level of consciousness. Older adults, particularly those with preexisting chronic medical conditions, are more likely to experience delirium or problems with consciousness. Nearly one-third of patients may have dysfunction after

discharge, and more than two-thirds of critically ill patients exhibit agitation and disorientation. These patients may present with encephalopathy and confusion. In addition, brain hemorrhages can cause a change in mental status. Toxic-metabolic encephalopathy, caused by systemic hyperinflammation, cerebrovascular events, seizures, and a possible CNS infection by SARS-CoV-2, results in changes in mental status in COVID-19 cases (MAGAR et al., 2022).

Seizure is a rapid, sporadic, abrupt, and uncontrolled electrical disturbance in nerve cell activity due to the elevated discharge of neurons in the brain. This causes changes in behavior, movements, and level of consciousness. They are characterized by loss of attention, impairment or loss of consciousness, skeletal muscle contraction, as well as partial and generalized seizures. Seizures have been observed to occur in the early phase of infection, and individuals with hypoxia are at increased risk of developing seizures. Acute frontal waves in an EEG (electroencephalogram) test performed on a patient with COVID-19 suggested sporadic epileptic abnormality, indicating a frontal epileptogenic dysfunction and suggesting the invasion of SARS-CoV-2 into the brain through the olfactory pathway (SINGH; SINGH, 2022).

Cerebrovascular accident (CVA) occurs when there is an interruption (ischemic case) of cerebral blood flow or when a cerebral vessel ruptures (hemorrhagic case), resulting in the death of neuronal cells due to lack of oxygen (MENDONÇA FILHO et al., 2023). Stroke is a neurological condition marked by focal deficits resulting from infarction or cerebral hemorrhage. Previous studies indicate that the risk of cerebrovascular events increased after COVID-19, with the incidence of ischemic stroke rising to nearly one in ten (or three in 100 in the first stroke) in individuals with encephalopathy. Recent studies have shown that the incidence of stroke in people infected with COVID-19 ranges between 0.9% and 2.7%. In adults, the incidence of COVID-19-related stroke has been reported to be up to 7.5 times higher than with influenza. SARS-CoV-2 can induce stroke by several mechanisms, including invasion of the vascular endothelium, which results in coagulopathy due to inflammation of the endothelium, cardiac injury, which generates clots, or instability of a preexisting atherosclerotic plaque. In addition, a significant reduction in platelet count and an increase in D-dimer levels have been observed in critically ill patients with COVID-19. In this scenario, the risk of blood vessel obstruction is considerably higher, which can lead to thrombosis in the arteries responsible for supplying blood to the brain (AHMED et al., 2022) (JHA et al., 2021) (VALDERAS et al., 2022) (MENDONÇA FILHO et al., 2023).

In many cases, the obstruction is not complete, but simply reducing blood flow to the brain can cause permanent damage to nerve tissue due to a lack of oxygen. In more severe

cases, total obstruction may occur, leading to malignancy and possibly death. In addition, the state of hypercoagulability can also trigger cerebral venous thrombosis. However, cases of this type are quite rare, although the relative risk is higher in patients with COVID-19. In Singapore, out of 206 patients with SARS-CoV, five were reported to have suffered a large vessel stroke. Of the four patients in serious condition, three died. In two of the patients, there was significant hypotension shortly before the onset of stroke, accompanied by disseminated intravascular coagulation (JHA et al., 2021) (MENDONÇA FILHO et al., 2023).

Additional evidence for neurological involvement in COVID-19 includes CSF examination, electrophysiological testing, and imaging results. The typical change in CSF after COVID-19 is the slight increase in cell count and protein levels, especially immunoglobulins, which suggests an inflammatory or infectious state. Regarding electrophysiology, two cases showed nonspecific alterations, another patient had focal seizures on the electroencephalogram, and the others had delayed nerve conduction, reduced amplitude of the action potential, and absence of F-waves, which is associated with damage to myelin and axons in Guillain-Barré Syndrome. MRI and CT scans have been widely used to look for signs of neurological disorders after COVID-19, such as inflammation and cerebrovascular dysfunction, suggesting direct invasion of SARS-CoV-2. In patients diagnosed with encephalitis, myelitis, meningitis, and Guillain-Barré Syndrome, enhancement of lesions in the meninges, brain, spinal cord, and nerve roots was visible on MRI, correlating with individual clinical manifestations (WANG et al., 2020).

CONCLUSION

Based on the evidence and discussions presented, SARS-CoV-2 infection is capable of triggering a series of neurological complications ranging from mild manifestations, such as headache and loss of smell, to severe conditions, such as encephalopathy, encephalitis, and stroke. The virus, when penetrating the central nervous system (CNS) through various routes, can cause inflammation, hypoxia and activation of exacerbated immune responses, contributing to direct and indirect neuronal damage. The cytokine storm, vascular endothelial invasion, and hypercoagulable state emerge as critical factors in the worsening of these neurological conditions. In addition, the involvement of the blood-brain barrier (BBB) and the activation of microglia reflect the complexity of the interactions between the virus and the CNS.

These findings underscore the importance of close clinical monitoring and early interventions for COVID-19 patients presenting with neurological signs, especially those

with pre-existing risk factors. A deeper understanding of the pathophysiological mechanisms underlying SARS-CoV-2 neuroinvasion may pave the way for more effective therapeutic approaches, aiming at both CNS protection and long-term management of neurological sequelae.

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