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ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM) ASSOCIATED WITH COVID-19

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Abstract: Objective Observe the relationship between Acute Disseminated Encephalomyelitis (ADEM) and COVID-19, focusing on its epidemiology and pathogenesis. **Methodology:** Narrative bibliographic review carried out using data obtained from PubMed, using the Boolean operators "OR" and "AND" in inclusion with the search terms "Acute Disseminated Encephalomyelitis", "COVID-19" and "Sars-CoV-2". Through the search, 203 articles were found that were submitted to the inclusion and exclusion criteria, and in the end 21 articles were selected. **Discussion:** The time relationship between COVID symptoms and ADEM manifestation is shorter when compared to other viral infections. SARS-COV has affinity with the Central Nervous System and has the ability to induce endothelial dysfunction, neuroinflammation and a state of hypercoagulation, in addition to damaging neurons. Confusion, lethargy, difficulty waking up from sedation, gait ataxia, pyramidal signs, seizures and involvement of peripheral nerves are some of the clinical signs of ADEM correlated to COVID-19. Studies also indicate an incidence of ADEM post-vaccination against COVID-19, with most cases appearing after the first dose. **Final considerations:** The presence of specific clinical manifestations and magnetic resonance imaging and laboratory findings support an early diagnosis. However, further research is needed on the pathological mechanisms involved between vaccination against COVID-19 and ADEM, in order to improve clinical management and optimize patient outcomes.

Keywords: Acute Disseminated Encephalomyelitis, COVID-19, Sars-CoV-2.

INTRODUCTION

Coronaviruses have been identified as infectious agents in humans and animals

for an extended period. At the end of 2019, a new mutant variant of this virus emerged in Wuhan, China, triggering serious cases of pneumonia (BROLA W.; WILSKI M., 2022). Although coronaviruses mainly affect the respiratory system, there is evidence of their ability to invade the Central Nervous System (CNS) (ALMQVIST J. et al., 2020). Symptoms prevalent in patients affected by SARS-CoV-2, the causal agent of COVID-19, include fever, cough, dyspnea, anosmia and myalgia. Recently, reports of associated neuropathologies have emerged, such as Acute Disseminated Encephalomyelitis (ADEM), revealed through radiographic examinations (REICHARD RR et al., 2020). ADEM, an immune-mediated demyelinating disorder of the CNS, has a higher incidence in children, with an average age of onset around 6.5 years (LEE S. et al., 2022).

The potential demyelination of the CNS by coronavirus, evidenced in previous animal models, suggests that SARS-CoV-2 may trigger neurological complications in previously healthy individuals and impact the course of several neurological conditions (REICHARD RR et al., 2020). Additionally, there are indications of incidence of ADEM after vaccination against COVID-19, highlighting a complex interaction between the virus, the immune response and the nervous system (LEE S. et al., 2022).

Elucidating the association between COVID-19 and ADEM is imperative to improve clinical management and mitigate associated risks. Analysis of this relationship becomes even more crucial given the reports of cases of post-vaccination ADEM, highlighting the need for robust research to discern the underlying mechanisms and foster effective treatment and prevention strategies (KORALNIK IJ; TYLER KL, 2020).

The central purpose of this study was to explore the correlation between Acute Disseminated Encephalomyelitis (ADEM) and COVID-19, focusing on epidemiology and pathogenesis. Through an integrative review, the aim is to elucidate the prevalence of cases and risk factors associated with post-COVID-19 ADEM, as well as unveil the pathological mechanisms involved, aiming to contribute to the evolution of diagnostic and therapeutic practices in the context of the interaction between viral infections and neurological disorders.

METHODOLOGY

This is a narrative bibliographic review developed according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. Used to prepare the research through its guiding question: "How does COVID-19 influence the incidence and pathogenesis of Acute Disseminated Encephalomyelitis (ADEM), and what are the clinical implications of this association?". The searches were carried out by searching the PubMed Central (PMC) database. The search terms were used in combination with the Boolean term "AND" and "OR" through the search strategy: (Acute Disseminated Encephalomyelitis) AND ((COVID-19) OR (Sars-CoV-2)). From this search, 203 articles were found, subsequently submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese and Spanish published between 2019 and 2023 and which addressed the themes proposed for this research, review and meta-analysis studies, observational studies, case reports, clinical trials, original studies made available in full. The exclusion criteria were: duplicate articles, available in abstract form, which did not directly address the proposal studied and which did not meet the other inclusion criteria. A total of 21 articles were selected to compose the present study.

DISCUSSION

Viral infections, including COVID-19, are known to affect the Central Nervous System (CNS), particularly in demyelinating diseases. The neuropathological manifestations of COVID-19 may result from direct viral invasion or a hyperinflammatory response induced by the infection, the latter being more common (REICHARD RR et al., 2020; FINSTERER J.; SCORZA FA, 2021). Potential routes of entry of SARS-CoV-2 into the CNS include retrograde axonal transport via the olfactory system and transport mediated by infected immune cells. The angiotensin-converting enzyme-2 (ACE2) facilitates the entry of the virus into cells by binding to the virus's Spike protein, which can cause cell death or endothelial dysfunction with inflammatory infiltrate (ARIÑO H. et al., 2022).

The immune response to COVID-19 involves a cytokine storm, with the release of cytokines and chemokines that affect the permeability of the blood-brain barrier and trigger neuroinflammatory cascades (FINSTERER J.; SCORZA FA, 2021). In the elderly, hyperinflammation is the main cause of neural impairment, while in young people, hypercoagulability is the predominant factor of neurological dysfunction, both linked to the immune response (KORALNIK IJ; TYLER KL; 2020).

The neurological complications of COVID-19 are varied, including fatigue, headache, olfactory/gustatory changes, ischemic stroke and severe inflammatory diseases of the CNS. Five categories of neurological complications must be monitored: cerebrovascular disorders, encephalopathies, post-infectious immune-mediated complications such as acute disseminated encephalomyelitis (ADEM), encephalitis (with possible seizures), and neuropsychiatric complications (ALMQVIST J. et al., 2020). In relation to pre-existing immune-mediated neurological diseases, it has been observed that Myasthenia Gravis and Guillain-Barré Syndrome are often exacerbated by the virus (MORAWIEC N. et al., 2023).

Acute disseminated encephalomyelitis (ADEM) is a rare neurological disease in which there is an autoimmune attack on the central nervous system. Reports link ADEM to COVID-19 infection, although the direct relationship is not yet completely clarified and confirmation that it is a post-infectious inflammatory process is still uncertain (ZELADA-RÍOS L. et al., 2021). However, the temporal proximity between COVID-19 symptoms and the onset of ADEM, shorter than the patterns described for other viral infections, reinforces the hypothesis of a clinical association between the two conditions (ESPÍNDOLA OM et al., 2021).

Nabizadeh F. et al. (2023) indicates an incidence of Acute Disseminated Encephalomyelitis (ADEM) post-vaccination against COVID-19, with most cases appearing after the first dose. The clinical spectrum of presentation varied significantly, including diverse neurological symptoms, with a minority of patients not responding favorably to treatment.

However, the conclusion of the study highlights the uncertainty of the causal relationship between vaccination and the development of ADEM, highlighting the need for more detailed investigations to clarify the pathogenesis and possible epidemiological correlation.

Epidemiologically, classic ADEM affects more children, while ADEM linked to COVID-19 affects more adults and the elderly, possibly due to the fact that SARS-CoV-2 infection is often asymptomatic or self-limited in children (ZELADA-RÍOS L. et al., 2021). Some studies have linked

ADEM to COVID-19 through evidence of exposure to the virus confirmed by PCR tests, in the absence of other etiological agents (ZELADA-RÍOS L. et al., 2021), while others have found difficulties in detecting viral RNA, resulting in numerous negative results (WANG Y. et al., 2022; PATERSON RW et al., 2020). This indicates the need for further neuropathological studies and specific serological tests to clarify the mechanisms involved (PATERSON RW et al., 2020).

Molecular investigations into human antibodies against SARS-CoV-2 highlighted antibodies with cross-reactivity not only with the virus' Spike protein, but also with the nucleoprotein and several human antigens, including neurofilaments involved in neurodegenerative processes (ZAMANI R. et al., 2022). CNS dysfunction may emerge early in the progression of COVID-19 due to viral infiltration, potentially explaining the early occurrence of neurological symptoms. Alternatively, during convalescence, a post-infectious immunological mechanism may induce autoimmunity due to molecular mimicry between viral and human antigens (STOIAN A. et al., 2023).

Vaccines can activate a cytotoxic immune response via T cells, with vaccine antigens being recognized by macrophages and monocytes, which trigger the release of inflammatory and pyrogenic cytokines, leading to an immune response similar to infection. This can result in neuroinflammation and microglial activation, depending on the immunogenetic makeup of the individual. Just like infection, vaccination can lead to CNS dysfunction through similar pathogenic mechanisms (STOIAN A. et al., 2023).

Therefore, evidence of CNS damage of immunological or immune-mediated origin suggests the risk of neuroinflammation subsequent to SARS-CoV-2 infection or vaccination, requiring expanded studies with epidemiological data to definitively determine the causal relationship with ADEM (STOIAN A. et al., 2023).

Diagnostic criteria for COVID-19-related ADEM are based on the presence of specific clinical symptoms, magnetic resonance imaging (MRI) findings, and laboratory tests. Common clinical signs include encephalopathy, ataxia, weakness in the limbs, pyramidal signs, convulsions and involvement of peripheral nerves, among others (WANG Y. et al., 2022; SRIWASTAVA S. et al., 2021; ESPÍNDOLA OM et al., 2021; ZELADA-RÍOS L. et al., 2021; MANZANO GS et al., 2021).

Cerebrospinal fluid (CSF) analysis often reveals inflammatory signs, and tests for specific antibodies can help with differential diagnosis (SRIWASTAVA S. et al., 2021; ZELADA-RÍOS L. et al., 2021; MANZANO GS et al., 2021; WANG Y. et al., 2022; PATERSON RW et al., 2020). For Sriwastava S. et al. (2021) in their recent observational review of the literature identified 43 cases of inflammatory disorders of the CNS, such as myelitis and ADEM, associated with COVID-19, with a tendency towards an association between the most severe forms of the disease and conditions such as acute hemorrhagic encephalomyelitis /necrotizing (AHNE/AHLE). This study highlights the importance of neuroimaging techniques and CSF analysis in early diagnosis, and suggests that, despite the low incidence, such neurological complications are significant and require further investigation. The results reinforce the need for continued surveillance for these disorders in patients with COVID-19, aiming to optimize clinical management and improve outcomes.

Therapy for post-COVID-19 ADEM generally follows established treatment for classic ADEM, involving the administration of intravenous methylprednisolone

and oral prednisone, with intravenous immunoglobulin and/or plasmapheresis as alternatives (WANG Y. et al., 2022; SRIWASTAVA S. et al., 2021; ESPÍNDOLA OM et al., 2021; ZELADA-RÍOS L. et al., 2021; MANZANO GS et al., 2021).

In a recent study involving 74 patients with Acute Disseminated Encephalomyelitis (ADEM), carried out by Stoian A. et al. (2023), it was observed that both COVID-19 infection and vaccination against SARS-CoV-2 can precede the development of the disease, with a significant portion progressing to acute hemorrhagic ADEM (AHLE). The research highlighted a correlation between the moderate form of COVID-19 and the occurrence of AHLE, and identified that adverse outcomes were associated with both clinical severities, manifested by coma and AHLE, and the use of more intensive immunomodulatory treatments. Despite these outcomes, the study reinforces the vital importance of vaccination in pandemic control, highlighting that the collective benefits of such public health programs outweigh the individual risks of complications. In line with this, Wang Y. et al. (2022) highlights the relationship between SARS-CoV-2 infection and severe neurological manifestations. Analysis of these cases revealed crucial demographic and epidemiological details, providing deeper insight into clinical characteristics and laboratory and imaging findings. This body of evidence suggests that although ADEM is a rare occurrence in patients with COVID-19, it represents a significant neurological complication, underscoring the importance of early recognition and appropriate intervention to improve clinical outcomes and inform future treatment strategies. This work highlights the need for continued surveillance and rapid treatment responses to optimize prognoses in cases of ADEM post-SARS-CoV-2 infection or vaccination.

FINAL CONSIDERATIONS

Acute disseminated encephalomyelitis (ADEM) is a rare and potentially serious neurological condition most prevalent in children but also seen in adults. Characterized by demyelinating inflammation that often occurs after viral infections or vaccination, ADEM represents a significant diagnostic and therapeutic challenge. Recent studies have indicated an incidence of ADEM in some patients after COVID-19 vaccination and after COVID-19 infection, who presented with various neurological symptoms due to damage to the central nervous system. ADEM investigation is based on the identification of specific clinical manifestations, complemented by MRI findings and laboratory analyses. The need for an early diagnosis is essential to initiate effective treatment and improve clinical results. However, current studies have not yet established a direct and definitive relationship between ADEM and vaccination against COVID-19, which highlights the importance of more comprehensive research. Such research must focus on the pathological mechanisms underlying ADEM and its possible correlation with vaccination against COVID-19. Understanding these mechanisms is crucial to improving the clinical management of patients and optimizing their outcomes. Furthermore, it is essential to investigate prevention strategies, risk management and specific therapeutic options for patients who develop ADEM, whether in a post-vaccination or post-infection context. It highlights the need for continued surveillance and rigorous clinical research to better understand ADEM, its triggers, and to develop effective treatment and prevention strategies. Collaboration between neurologists, epidemiologists and infectious disease specialists is vital to advance our understanding of and response to this challenging disease.

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