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ANTIVIRAL THERAPY AND MANAGEMENT OF COMPLICATIONS IN THE TREATMENT OF HERPETIC ENCEPHALITIS

TERAPIA ANTIVIRAL E MANEJO DAS COMPLICAÇÕES NO TRATAMENTO DA ENCEFALITE HERPÉTICA

TERAPIA ANTIVIRAL Y MANEJO DE LAS COMPLICACIONES EN EL TRATAMIENTO DE LA ENCEFALITIS HERPÉTICA

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ABSTRACT

The management of Herpes Simplex Encephalitis (HSE) requires advancing beyond the mere eradication of viral load. Although intravenous acyclovir remains the unquestionable cornerstone of treatment, its effectiveness is intrinsically limited by the timing of administration—ideally within the first 24 to 48 hours—and by its inability to prevent biological damage independent of viral replication. The persistence of sequelae in up to 70% of survivors highlights that virological control does not guarantee neurological preservation. The pathogenesis involves sustained activation of the TNF/NF-κB inflammatory pathway and the identification of ferroptosis (iron-dependent cell death driven by lipid peroxidation) as a key event, suggesting new adjuvant therapeutic targets such as ferroptosis inhibitors. Long-term complications, such as post-herpetic autoimmune encephalitis, occur in approximately 25% to 27% of patients and require rapid intervention with aggressive immunotherapy. The discovery that around 10% of sporadic pediatric HSE cases originate from inborn errors of immunity (defects in the TLR3 pathway and type I interferon signaling) underscores the need for genomic surveillance to support precision medicine strategies. In summary, the future of HSE treatment lies in the implementation of multimodal protocols that integrate genetic and immunological diagnostics with early virological control, combining antivirals with neuroprotective and immunomodulatory agents.

Keywords: Herpetic Encephalitis. Antiviral Therapy. Acyclovir. Ferroptosis. Autoimmune Encephalitis. Immunomodulation.

RESUMO

O manejo da encefalite herpética (HSE) exige uma evolução para além da simples erradicação da carga viral. Embora o aciclovir intravenoso permaneça como o pilar

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inquestionável do tratamento, sua eficácia é intrinsecamente limitada pela janela temporal de administração, sendo ideal o início da terapia nas primeiras 24 a 48 horas, e pela incapacidade de conter danos biológicos independentes da replicação viral. A persistência de sequelas em até 70% dos sobreviventes evidencia que o controle virológico não garante a preservação neurológica. A patogênese envolve a ativação persistente da via inflamatória TNF/NF-kB e a identificação da ferroptose (morte celular iron-dependente por peroxidação lipídica) como um evento-chave, sugerindo novos alvos terapêuticos adjuvantes, como inibidores de ferroptose. Complicações de longo prazo, como a encefalite autoimune pós-herpética, manifestam-se em aproximadamente 25% a 27% dos pacientes e exigem intervenção rápida com imunoterapia agressiva. A descoberta de que cerca de 10% dos casos infantis de HSE esporádica têm origem em erros inatos da imunidade (defeitos na via do TLR3 e do interferon tipo I) reforça a necessidade de vigilância genômica para estratégias de medicina de precisão. Em síntese, o futuro do tratamento da encefalite herpética reside na implementação de protocolos multimodais que integrem diagnósticos genéticos e imunológicos ao controle virológico precoce, combinando antivirais com agentes neuroprotetores e imunomoduladores.

Palavras-chave: Encefalite Herpética. Terapia Antiviral. Aciclovir. Ferroptose. Encefalite Autoimune. Imunomodulação.

RESUMEN

El manejo de la encefalitis herpética (HSE) requiere avanzar más allá de la simple erradicación de la carga viral. Aunque el aciclovir intravenoso sigue siendo el pilar incuestionable del tratamiento, su eficacia está intrínsecamente limitada por la ventana temporal de administración—siendo ideal iniciar la terapia dentro de las primeras 24 a 48 horas—y por su incapacidad para contener daños biológicos independientes de la replicación viral. La persistencia de secuelas en hasta el 70% de los sobrevivientes evidencia que el control virológico no garantiza la preservación neurológica. La patogénesis implica la activación persistente de la vía inflamatoria TNF/NF-κB y la identificación de la ferroptosis (muerte celular dependiente del hierro por peroxidación lipídica) como un evento clave, lo que sugiere nuevos objetivos terapéuticos adyuvantes, como los inhibidores de la ferroptosis. Las complicaciones a largo plazo, como la encefalitis autoinmune postherpética, se presentan en aproximadamente el 25% al 27% de los pacientes y requieren una intervención rápida con inmunoterapia agresiva. El descubrimiento de que alrededor del 10% de los casos pediátricos esporádicos de HSE tienen origen en errores innatos de la inmunidad (defectos en la vía del TLR3 y del interferón tipo I) refuerza la necesidad de vigilancia genómica para estrategias de medicina de precisión. En síntesis, el futuro del tratamiento de la encefalitis herpética radica en la implementación de protocolos multimodales que integren diagnósticos genéticos e inmunológicos con el control virológico precoz, combinando antivirales con agentes neuroprotectores e inmunomoduladores.

Palabras clave: Encefalitis Herpética. Terapia Antiviral. Aciclovir. Ferroptosis. Encefalitis Autoinmune. Inmunomodulación.

1 INTRODUCTION

Herpes simplex virus (HSE) encephalitis is the leading cause of sporadic, non-epidemic viral encephalitis in the developed world, characterized by a severe necrotizing infection of the brain parenchyma (Cleaver et al., 2024; Zhang and Casanova, 2024). Although the advent of intravenous acyclovir has significantly reduced mortality—from approximately 70% to about 15% to 20%—morbidity remains alarming, with most survivors experiencing persistent neurological and cognitive sequelae (Poussier et al., 2024; Rybak-Wolf et al., 2023). The pathogenesis of HSE is complex, involving both direct viral cytopathic damage and an exacerbated inflammatory host response, which often persists even after viral replication is controlled (Zhang et al., 2023; Rybak-Wolf et al., 2023).

Current clinical management faces critical challenges, notably the need for immediate initiation of antiviral therapy and the recognition of late complications such as postherpetic autoimmune encephalitis (Cleaver et al., 2024; Poussier et al., 2024). Recent evidence suggests that vulnerability to disease may have genetic underpinnings, particularly in children with inborn errors of central nervous system intrinsic immunity, which paves the way for precision medicine approaches (Zhang and Casanova, 2024). In addition, the discovery of novel cell death pathways, such as virus-induced ferroptosis, suggests that future treatment should integrate antivirals with neuroprotective and immunomodulatory agents (Xu et al., 2023). Given the severity of the condition and the impact on functional outcomes, ongoing analysis of therapeutic protocols and complication management is imperative (Poussier et al., 2024; Cleaver et al., 2024).

Herpetic encephalitis is a neuroinfection caused mainly by the herpes simplex virus (HSV-1) and affects a large part of the human population worldwide. HSV-1 is the most common pathogen of infectious encephalitis in children and adults (Rybak-wolf et al., 2023), followed by varicella-zoster virus (VZV). These viruses are associated with high mortality and morbidity rates, especially in immunosuppressed individuals, as the sequelae prevent full recovery in 30% of patients with herpetic herpetic encephalitis simplex (EHS) and 50% of patients with varicella-zoster encephalitis (EVZ) (Poussier et al., 2024).

Despite therapeutic advances, encephalitis has a high degree of virulence in all age groups, with a mortality rate in more than 70% of patients without pharmacological treatment with acyclovir and with mild to severe neurological and cognitive sequelae in

about 40 to 60% of non-fatal cases treated with antivirals (Zhang et al., 2024). Thus, there is a need to understand the therapies and management of the complications of the disease.

From this perspective, the use of acyclovir (a first-choice antiviral) that suspends viral replication, but does not prevent an immune response with deleterious effects on the brain parenchyma (Cleaver et al., 2024; Rybak-Wolfn et al., 2023), stands out as the main treatment strategy for simple herpetic encephalitis. As a result, the morbidity and mortality rates of simple herpetic encephalitis are high, with most surviving patients presenting severe neurological sequelae despite the use of antiviral therapy (Xu et al., 2022).

The mechanisms involved in the pathogenesis of neurological diseases induced by HSV-1 are not fully understood, studies indicate that ferroptosis (a non-apoptotic form of programmed cell death), amplification of tumor necrosis factor signaling, synaptic dysfunction, and destructuring of dendritic spines are fundamental pieces in neuroinflammation induced by viral replication. The interaction of these mechanisms contributes in a timely manner to brain tissue damage (Rybak-Wolf et al., 2023; Xu et al., 2022).

Understanding the immunopathophysiological processes of herpetic neuroinfection is needed to elucidate why antiviral treatment alone or in combination with other anti-inflammatory drugs show promising results, although the prognosis still remains unsatisfactory (Zhang et al., 2024; Poussier et al., 2023; Rybak-Wolf et al., 2023).

In this sense, through a narrative review, the objective was to synthesize and analyze antiviral therapy and the management of complications in the treatment of herpetic encephalitis.

2 METHODOLOGY

The present study is characterized as a narrative literature review, developed with the objective of synthesizing and analyzing the most recent scientific evidence related to antiviral therapy and the management of complications in the treatment of herpetic encephalitis. The search was carried out in the PubMed database, using the descriptors "Encephalitis, Herpes Simplex" and "Therapeutics", combined using the Boolean operators AND and OR, according to the Medical Subject Headings (MeSH) terminology. Articles published in the last five years, fully available and written in Portuguese or

English, that directly addressed the topic were included. Studies that did not have a direct relationship with the central theme, duplicate publications, narrative reviews with low methodological rigor, and articles not indexed in the database used were excluded. The selection of studies was conducted in two stages: screening of titles and abstracts, followed by the evaluation of full texts to confirm relevance. The information extracted was organized in a descriptive manner.

3 RESULTS

Contemporary scientific literature reaffirms that intravenous acyclovir is the absolute standard of care for SEH. Prospective cohort studies indicate that the time elapsed between hospital admission and initiation of acyclovir is the main determinant of prognosis, with delays greater than 24-48 hours being strongly associated with worse functional outcomes and higher mortality. In addition to the time of antiviral initiation, the dose and duration of treatment have been shown to be important for favorable clinical outcomes. (Poussier et al., 2024). However, experimental models in human brain organoids have shown that while acyclovir effectively disrupts HSV-1 replication, it does not prevent secondary tissue damage in up to half of survivors, such as loss of neuroepithelial integrity and degeneration of neuronal processes driven by excessive activation of tumor necrosis factor (TNF). (Rybak-Wolf et al., 2023).

Glucocorticoids, immunoglobulin use, and rituximab have significant effects on cases of post-HSE autoimmune encephalitis, which can present in up to 5 to 27% of patients, usually within the first two months after diagnosis of infection. In this scenario, it is important to distinguish the autoimmune picture from a recurrence of the herpetic picture (rare, confirmed by CSF PCR).

In the field of complications and mechanisms of injury, significant advances have been documented in the identification of ferroptosis—a form of iron-dependent programmed cell death characterized by lipid peroxidation—as a key event in the pathogenesis of HSE (Xu et al., 2023). In CNS HSV infection, activation of innate immunity generates oxidative stress that dysregulates iron metabolism, increasing free iron and promoting lipid peroxidation, triggering ferroptosis. Simultaneously, the reduction of antioxidants such as glutathione and GPX4 compromises cell defense, intensifying membrane damage. Thus, ferroptosis acts as a mechanism of secondary neuronal death, potentiating inflammation-mediated tissue injury and contributing to the clinical severity

and neurological sequelae observed in herpetic encephalitis (Xu et al., 2023). These findings suggest that therapeutic interventions targeting the modulation of oxidative stress and iron metabolism may represent promising adjuvant strategies in the management of this condition. The use of ferroptosis inhibitors, such as Liproxstatin-1, has demonstrated in animal models the ability to reduce neuroinflammation and cerebral edema, suggesting a promising adjuvant therapeutic target (Xu et al., 2023). These findings reinforce that the pathogenesis of herpetic encephalopathy is not restricted to the direct cytopathic effect of the virus, but involves complex immune-mediated mechanisms that play a determining role in the clinical evolution and prognosis of the disease.

Additionally, genomic surveillance has revealed that up to 10% of childhood HSE cases can be explained by defects in genes of the TLR3 pathway and the type I interferon circuit, which compromise the intrinsic immunity of neurons and oligodendrocytes against the virus (Zhang and Casanova, 2024). These defects correspond, in large part, to monogenic inborn errors distributed in at least 19 genes already identified, many with autosomal recessive inheritance and incomplete clinical penetrance, which explains the sporadic character of the disease even in the face of a defined genetic basis. Mechanistically, these alterations affect critical steps of the antiviral response, resulting in insufficient production of IFN-α/β and failure to induce interferon-stimulated genes. (Zhang and Casanova, 2024). As a consequence, resident cells of the central nervous system, especially cortical neurons and oligodendrocytes, become highly permissive to HSV-1 replication, with increased viral load and cell death, a phenomenon that can be partially reversed in vitro by exogenous administration of type I interferon. It is important to highlight that this susceptibility is tissue-specific, not observed in peripheral nervous system cells or leukocytes, which reinforces the concept that HSE results primarily from failures in brain intrinsic immunity, and not from classic systemic immunodeficiencies. (Zhang and Casanova, 2024).

In the management and complementary follow-up of the patient, it is important to value renal monitoring, due to the risk of acyclovir crystallization in the renal tubules and imminence of acute renal failure, in addition to neuropsychological screening and immunological surveillance, in view of the possible cognitive sequelae and risk of autoimmune encephalitis, even after appropriate treatment (Poussier et al., 2024).

4 DISCUSSION

The discussion about the treatment of HSE has evolved to the understanding that clearance of the virus is only the first step in management. A critical phenomenon discussed is postherpetic autoimmune encephalitis, where viral infection triggers the production of autoantibodies against synaptic receptors such as the NMDA receptor (anti-NMDAr) (Cleaver et al., 2024). This condition often manifests as a neurological or psychotic relapse after completion of initial antiviral treatment, requiring immediate institution of immunotherapy with corticosteroids, immunoglobulins, or rituximab (Cleaver et al., 2024; Rybak-Wolf et al., 2023). Integration of immunological diagnostics is vital to distinguish viral persistence from autoimmune inflammation (Cleaver et al., 2024).

Another central point of debate refers to the insufficiency of acyclovir in preventing long-term sequelae. The persistence of elevated levels of proinflammatory cytokines and chronic microglial activation suggest that the therapeutic window for immunomodulatory interventions should be better defined (Zhang et al., 2023; Rybak-Wolf et al., 2023). The efficacy of combining acyclovir with corticosteroids to reduce cerebral edema still lacks definitive evidence from large-scale randomized controlled trials, although its use is frequent in clinical practice (Cleaver et al., 2024). The future prognosis of HSE therefore lies in multimodal protocols that combine early virological control, protection against non-apoptotic forms of cell death, and aggressive management of postviral immune dysregulation (Poussier et al., 2024; Xu et al., 2023).

In addition, recent experimental evidence reinforces that neurological damage in herpetic encephalitis is not exclusively dependent on viral load, but results from a complex interaction between viral replication and host inflammatory response. Models in human brain organoids have demonstrated that although acyclovir effectively disrupts HSV-1 replication, there is persistence of neuronal structural and functional changes, including synaptic dysfunction and loss of neuroepithelial integrity. This finding supports the hypothesis that inflammatory pathways, especially those mediated by TNF and NF-κB activation, play a central role in the progression of brain damage, even after virologic control, which limits the efficacy of antiviral treatment alone (RYBAK-WOLF et al., 2023).

Another relevant aspect refers to ferroptosis as an emerging mechanism in the pathophysiology of HSE. Studies have shown that HSV-1 infection induces intracellular iron accumulation, increased reactive oxygen species, and lipid peroxidation, culminating in non-apoptotic neuronal cell death. This process is directly associated with the

intensification of neuroinflammation and the worsening of the clinical picture. Modulation of this pathway, through ferroptosis inhibitors or strategies that preserve Nrf2 function, emerges as a promising therapeutic approach, capable not only of reducing tissue damage, but also of potentially interfering with viral replication and the subsequent inflammatory cascade (XU et al., 2023).

In the immunological context, the importance of the innate and adaptive immune response is highlighted both in containing the infection and in the genesis of late complications. The activation of pattern recognition receptors, such as TLR3 and cytosolic viral DNA sensors, triggers the production of interferons and pro-inflammatory cytokines essential for viral control, but potentially deleterious to neural tissue. In parallel, the disruption of the blood-brain barrier and the exposure of neuronal antigens favor the activation of B and T lymphocytes, culminating in the production of autoantibodies and the development of post-infectious autoimmune encephalitis. This delicate balance between antiviral defense and immune damage reinforces the need for more targeted therapeutic approaches (ZHANG et al., 2023).

Finally, the clinical heterogeneity of HSE can also be explained by host genetic factors, especially inborn errors of immunity related to the type I interferon pathway. The identification of these defects, particularly in young patients or those with disease recurrence, opens space for precision medicine strategies, with potential prognostic and therapeutic impact. In this scenario, the future of herpetic encephalitis management will depend on the integration of early diagnosis, immediate antiviral therapy, and personalized adjuvant interventions, capable of modulating the inflammatory response, preventing cell death, and reducing long-term neurological sequelae (ZHANG; CASANOVA, 2024).

5 CONCLUSION

The systematic analysis of the scientific evidence allows us to conclude that the management of herpetic encephalitis (HSE) requires an evolution beyond the simple eradication of the viral load. Although intravenous acyclovir remains the unquestionable pillar of treatment, drastically reducing mortality, its efficacy is intrinsically limited by the time window of administration and the inability to contain biological damage independent of viral replication. The initiation of therapy should ideally occur within the first 24 to 48 hours after admission, since delays longer than this period are strongly correlated with

increased morbidity and mortality. In this context, early differentiation between LVSH and varicella-zoster encephalitis (LVEV) is imperative, given the significantly superior aggressiveness of HSV-1 to the brain parenchyma compared to the vascular pathophysiology of VZV.

The persistence of sequelae in up to 70% of survivors shows that virological control does not guarantee neurological preservation. Experimental models demonstrate that the degeneration of neuronal processes and the loss of neuroepithelial integrity are driven by the persistent activation of the TNF pathway via NF-kB, an inflammatory process that acyclovir cannot interrupt. In addition, the identification of ferroptosis (iron-dependent cell death by lipid peroxidation) as a key event in pathogenesis suggests new adjuvant therapeutic targets, such as the use of ferroptosis inhibitors or Nrf2 agonists to mitigate neuroinflammation and cerebral edema.

Long-term complications and individual vulnerability also redefine modern management. Postherpetic autoimmune encephalitis, often associated with anti-NMDAr antibodies, presents in approximately 25% to 27% of patients, requiring clinical surveillance and rapid intervention with aggressive immunotherapy. Simultaneously, the finding that about 10% of childhood cases of sporadic HSE originate from inborn errors of immunity (such as defects in the TLR3 and interferon type I pathway) reinforces the need for genomic surveillance for precision medicine strategies.

In summary, the future of herpetic encephalitis treatment lies in the implementation of multimodal protocols that integrate genetic and immunological diagnostics with early virological control. The combination of antivirals with neuroprotective and immunomodulatory agents represents the fundamental way to reduce the burden of permanent neurological sequelae and improve the quality of life and functional prognosis of survivors.

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