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THERAPEUTIC PROTOCOLS AND MANAGEMENT OF NEUROLOGICAL MANIFESTATIONS IN THE TREATMENT OF HEPATIC ENCEPHALOPATHY

PROTOCOLOS TERAPÊUTICOS E MANEJO DAS MANIFESTAÇÕES NEUROLÓGICAS NO TRATAMENTO DA ENCEFALOPATIA HEPÁTICA

PROTOCOLOS TERAPÉUTICOS Y MANEJO DE LAS MANIFESTACIONES NEUROLÓGICAS EN EL TRATAMIENTO DE LA ENCEFALOPATÍA HEPÁTICA

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ABSTRACT

Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome mediated by dysfunction of the gut-liver-brain axis, in which hyperammonemia and intestinal dysbiosis promote neuroinflammation and astrocytic edema. This study conducted a narrative literature review (PubMed, last five years) aiming to analyze therapeutic protocols and the management of neurological manifestations of the condition. The findings confirm lactulose as the cornerstone therapy, while rifaximin — especially in combination therapy — demonstrates superiority in maintaining remission and reducing hospitalizations. Emerging microbiome modulation strategies, such as probiotics and fecal microbiota transplantation, appear promising for restoring intestinal integrity. In neurological management, adjuvant therapies such as L-ornithine L-aspartate (LOLA) and albumin infusion stand out. In pediatrics, monitoring must be rigorous due to the risk of rapid progression to cerebral edema. It is concluded that HE management requires a multidisciplinary and individualized approach focused on reducing nitrogen load and modulating the intestinal environment to optimize prognosis and patients' quality of life.

Keywords: Hepatic Encephalopathy. Rifaximin. Lactulose. Intestinal Microbiota. Therapeutics.

RESUMO

A encefalopatia hepática (EH) é uma síndrome neuropsiquiátrica complexa mediada pela disfunção do eixo intestino-fígado-cérebro, na qual a hiperamonemia e a disbiose intestinal promovem neuroinflamação e edema astrocitário. Este estudo realizou uma revisão narrativa da literatura (PubMed, últimos cinco anos) com o objetivo de analisar os protocolos terapêuticos e o manejo das manifestações neurológicas da condição. Os

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achados confirmam a lactulose como terapia de base, enquanto a rifaximina — especialmente em terapia combinada — demonstra superioridade na manutenção da remissão e redução de hospitalizações. Estratégias emergentes de modulação do microbioma, como probióticos e o transplante de microbiota fecal, apresentam-se promissoras para restaurar a integridade intestinal. No manejo neurológico, destacam-se adjuvantes como a L-ornitina L-aspartato (LOLA) e a infusão de albumina. Na pediatria, a vigilância deve ser rigorosa devido ao risco de rápida progressão para edema cerebral. Conclui-se que o manejo da EH exige uma abordagem multidisciplinar e individualizada, focada na redução da carga nitrogenada e na modulação intestinal para otimizar o prognóstico e a qualidade de vida dos pacientes.

Palavras-chave: Encefalopatia Hepática. Rifaximina. Lactulose. Microbiota Intestinal. Terapêutica.

RESUMEN

La encefalopatía hepática (EH) es un síndrome neuropsiquiátrico complejo mediado por la disfunción del eje intestino-hígado-cerebro, en el cual la hiperamonemia y la disbiosis intestinal promueven neuroinflamación y edema astrocitario. Este estudio realizó una revisión narrativa de la literatura (PubMed, últimos cinco años) con el objetivo de analizar los protocolos terapéuticos y el manejo de las manifestaciones neurológicas de la condición. Los hallazgos confirman a la lactulosa como terapia de base, mientras que la rifaximina — especialmente en terapia combinada — demuestra superioridad en el mantenimiento de la remisión y la reducción de hospitalizaciones. Las estrategias emergentes de modulación del microbioma, como los probióticos y el trasplante de microbiota fecal, se presentan como prometedoras para restaurar la integridad intestinal. En el manejo neurológico, se destacan coadyuvantes como la L-ornitina L-aspartato (LOLA) y la infusión de albúmina. En pediatría, la vigilancia debe ser rigurosa debido al riesgo de rápida progresión hacia edema cerebral. Se concluye que el manejo de la EH requiere un enfoque multidisciplinario e individualizado, centrado en la reducción de la carga nitrogenada y en la modulación intestinal para optimizar el pronóstico y la calidad de vida de los pacientes.

Palabras clave: Encefalopatía Hepática. Rifaximina. Lactulosa. Microbiota Intestinal. Terapéutica.

1 INTRODUCTION

Hepatic encephalopathy (HE) is a severe and debilitating neuropsychiatric complication arising from acute or chronic liver disease as well as portosystemic shunts. The condition manifests itself in a continuous spectrum, ranging from minimal or hidden forms — marked by subtle cognitive deficits and alterations in the sleep-wake cycle — to open and severe conditions, which include neuromotor dysfunction, lethargy and coma (Bass et al., 2010; Luo et al., 2023). It is a syndrome that imposes a significant burden on patients, caregivers, and health systems, and is strongly associated with increased hospitalization rates and a poorer overall survival prognosis (Bass et al., 2010; Buckholz & Brown, 2024).

The pathophysiological basis of HS is complex and multifactorial, and is widely understood through the dysfunction of the gut-liver-brain axis. Hepatic failure and portosystemic shunts allow gut-derived neurotoxins, primarily ammonia, to escape hepatic metabolism and cross the blood-brain barrier. In the brain, ammonia is converted to glutamine inside astrocytes, generating an osmotic gradient that results in astrocyte edema, oxidative stress, and neuroinflammation (Buckholz & Brown, 2024; Luo et al., 2023; Bartlett & Kohli, 2024). In addition, the state of intestinal dysbiosis and the failure of the mucosal barrier favor bacterial translocation and endotoxemia, which act in synergy with ammonia to exacerbate brain toxicity (Bloom et al., 2021).

In this context, recent studies demonstrate that the pathophysiology of hepatic encephalopathy involves broader mechanisms than just isolated hyperammonemia. Changes in the gut microbiota, increased permeability of the intestinal barrier, and activation of neuroinflammatory processes have been recognized as important factors for the development and worsening of the neurological manifestations of the disease (Luo et al., 2023; Bloom et al., 2021). In addition, new therapeutic approaches have been investigated with the aim of reducing not only acute episodes of decompensation, but also the persistent cognitive impacts associated with hepatic encephalopathy, contributing to prognostic and functional improvement of patients (Buckholz & Brown, 2024).

In addition to acute neurologic manifestations, recent evidence indicates that recurrent episodes of hepatic encephalopathy can cause persistent cognitive deficits, even after clinical recovery. Patients with HS may experience long-lasting impairment of memory, attention, psychomotor speed, and executive functions, with a significant impact

on quality of life and social reintegration (Buckholz & Brown, 2024). In children, the diagnosis becomes even more challenging due to the variability of clinical manifestations according to age and neurocognitive development, requiring close follow-up to prevent cerebral edema and systemic deterioration (Bartlett & Kohli, 2024).

2 METHODOLOGY

The present investigation is a narrative review of the literature, structured with the purpose of compiling and examining contemporary scientific evidence regarding therapeutic protocols and the management of hepatic encephalopathy. The search for data was conducted in the PubMed database, using the descriptors 'Hepatic Encephalopathy' and 'Therapeutics', duly articulated through the Boolean operators AND and OR, in line with the structured vocabulary of the Medical Subject Headings (MeSH). The inclusion criterion included studies published in full in the last five years (with the exception of essential historical landmarks provided), written in English or Portuguese, which dealt directly with the proposed theme. Publications that were outside the main scope, duplicate articles, reviews of poor methodological rigor, and studies not indexed in this database were discarded. The screening of the research occurred in two distinct phases: first, titles and abstracts were read; Then, the full text was evaluated in full to attest to its relevance. The extracted data were finally synthesized and exposed under a descriptive approach.

3 RESULTS AND DISCUSSION

The therapeutic management of HS is mainly based on reducing the nitrogen load and modulating the gut microbiome to mitigate neurotoxicity. Historically, nonabsorbable disaccharides, notably lactulose, have been the mainstay of first-line treatment. Lactulose works by reducing colonic pH and promoting a cathartic effect, which inhibits the growth of ammonia-producing bacteria and decreases their systemic absorption (Bloom et al., 2021; Buckholz & Brown, 2024). However, adherence to this therapy is often hampered by its gastrointestinal adverse effects, such as bloating, flatulence, and unpredictable diarrhea (Bass et al., 2010; Buckholz & Brown, 2024).

To overcome these limitations and improve outcomes, rifaximin—a broad-spectrum oral antibiotic with minimal systemic absorption—has established itself as a crucial therapeutic advance. Unlike systemic antibiotics that carry risks of nephrotoxicity

or ototoxicity, rifaximin is safe for long-term use and has a low risk of inducing bacterial resistance (Bass et al., 2010). Evidence shows that rifaximin alters bacterial metabolism and reduces endotoxemia and systemic inflammation, promoting effective maintenance of remission and drastically reducing the risk of hospitalizations (Bass et al., 2010; Bloom et al., 2021). The combined lactulose and rifaximin approach has been shown to be superior to lactulose monotherapy, providing significantly higher rates of clinical efficacy and a substantial reduction in mortality risk (Fu et al., 2022).

In addition to established therapies, the direct modulation of the microbiome via prebiotics, probiotics, and synbiotics has gained prominence. Probiotics (such as *Lactobacillus* and *Bifidobacterium* strains) help restore the integrity of the intestinal barrier, decrease the translocation of lipopolysaccharides (LPS), and modulate the systemic immune response, reversing minimal HS in several patients (Bloom et al., 2021; Luo et al., 2023). In cases of refractory dysbiosis, Fecal Microbiota Transplantation (FMT) emerges as an innovative strategy. Preliminary studies indicate that FMT may improve cognition and reduce episodes of open HS, possibly by increasing short-chain fatty acid production and restoring bile acid metabolism, although logistical challenges and infectious risks still require standardization (Bloom et al., 2021; Luo et al., 2023; Buckholz & Brown, 2024).

The expansion of knowledge about the pathophysiology of hepatic encephalopathy (HS), especially involving the gut-liver-brain axis, has driven the study of new therapeutic strategies. Among them, albumin infusion stands out, which has anti-inflammatory properties and potential to reduce serum ammonia levels. In addition, urea cycle modulators, such as L-ornithine L-aspartate (LOLA), and agents that favor urinary ammonia excretion, such as ornithine phenylacetate and glycerol phenylbutyrate, offer alternative pathways for ammonia detoxification. Another therapeutic line involves modulation of neurotransmitters related to hyperammonemia-induced neuroinflammation, including GABA-A receptor antagonists, L-carnitine, and flumazenil, with potential cognitive benefit. While many of these approaches still require more evidence for application in clinical practice, the diversity of therapies reinforces the prospect of a more individualized approach directed at the multifactorial nature of HS (Buckholz & Brown, 2024).

Finally, the management of HS requires increased attention in pediatric populations. In children, symptoms are often subtle—such as irritability, mood swings,

and difficulty concentrating at school—and standardized psychometric assessment tools for adults are difficult to apply (Bartlett & Kohli, 2024). Rapid progression to cerebral edema is a severe threat, especially in acute liver failure. Treatment in children follows the principles of ammonia reduction with lactulose and rifaximin, but severe conditions may require extracorporeal liver support (CRRT) to manage toxin accumulation and the imminent risk of brain herniation (Bartlett & Kohli, 2024).

4 CONCLUSION

Hepatic encephalopathy is a multifactorial neuropsychiatric complication associated with an important clinical, functional, and prognostic impact in patients with liver disease. The advancement of knowledge about the gut-liver-brain axis has allowed us to understand that the pathophysiology of HS goes beyond isolated hyperammonemia, also involving intestinal dysbiosis, neuroinflammation and changes in intestinal permeability, factors directly related to the neurological manifestations of the disease.

In this context, the therapeutic protocols currently used, especially lactulose and rifaximin, remain fundamental pillars in the clinical management of hepatic encephalopathy, contributing to the control of neurological symptoms, reduction of recurrences, and reduction of hospitalizations. At the same time, emerging strategies aimed at modulating the gut microbiota, such as probiotics and fecal microbiota transplantation, show promising potential as adjuvant therapies, although they still require further scientific consolidation for wide clinical application.

Thus , the management of the neurological manifestations of hepatic encephalopathy requires a multidisciplinary and individualized approach, aimed not only at reducing the nitrogen load, but also at controlling the inflammatory processes and intestinal changes associated with the disease, aiming to improve the prognosis and quality of life of patients.

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