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Original Research Article

Impact of Helicobacter pylori Infection on the Pathogenesis of Minimal Hepatic Encephalopathy and the Effects of Its Eradication

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Abstract:

Background: Hepatic encephalopathy (HE) is a neuropsychiatric disorder associated with liver failure, while minimal hepatic encephalopathy (MHE) represents its initial and mild stage. MHE results from cognitive and psychomotor disorders primarily induced by hyperammonemia. The gastrointestinal bacterium Helicobacter pylori (H. pylori), which secretes urease and contributes to ammonia generation, may exacerbate MHE.

Aim: This research examines the effects of H. pylori infection on MHE and the effects of its eradication on metabolic parameters and cognitive function.

Methodology: A prospective observational study involving 75 patients diagnosed with cirrhosis, of which 40 presented with minimal hepatic encephalopathy (MHE). Patients were subjected to psychometric assessments, fasting blood ammonia measurements, and H. pylori identification through rapid urease tests. MHE patients underwent two weeks of triple therapy for H. pylori eradication and were subsequently re-evaluated after four weeks.

Results: Pre-treatment levels of ammonia were significantly higher in H. pylori-positive patients (1.82 ± 0.30 µg/mL) compared to H. pylori-negative patients (1.38 ± 0.15 µg/mL). Following eradication, ammonia levels decreased significantly (1.20 ± 0.25 µg/mL), which was associated with improved psychometric functioning ($p < 0.001$). The results indicate that H. pylori are involved in the pathogenesis of MHE via systemic ammonia elevation and neurocognitive impairment.

Conclusion: H.pylori eradication considerably improves biochemical and neuropsychometric indicators, suggesting that it could be a treatment target for MHE. Confirmation of the results is necessary, and the long-term effects require further investigation. The eradication of H. pylori may serve as an innovative approach to prevent the progression of minimal hepatic encephalopathy (MHE) and enhance patient outcomes.

Keywords: Ammonia Levels, Cirrhosis, Helicobacter Pylori, Hepatic Encephalopathy, Hyperammonemia, Minimal Hepatic Encephalopathy, Psychometric Performance.

Introduction

"Hepatic encephalopathy (HE) is a significant neuropsychiatric disorder associated with liver failure, especially in individuals with cirrhosis. This encompasses a broad range of neurological impairments, from minimal hepatic encephalopathy (MHE) to deep coma and potentially death [1]. Mild hepatic encephalopathy (MHE) represents an early and less severe variant of HE, characterized by subtle cognitive and psychomotor deficits that can only be identified through sophisticated neuropsychometric assessments, including Electroencephalograms (EEG), line tracing tests, number connection tests (NCT), figure connection tests (FCT), and evoked potentials [2]. MHE poses diagnostic challenges during clinical interviews; however, its identification is clinically important as it signifies compromised daily functioning and a heightened risk of advancing to overt HE [3].

Hyperammonemia is a significant biochemical abnormality in chronic hepatic encephalopathy, wherein elevated blood ammonia levels contribute to the neurological manifestations of the condition [4]. The increase in ammonia levels is due to multiple factors, including compromised liver detoxification and increased ammonia production in the gut. Helicobacter pylori, a gram-negative rod that colonizes the gastric mucosa, is associated with ammonia production because of its significant urease activity [5]. The enzyme catalyzes the hydrolysis of urea into ammonia and carbon dioxide, resulting in elevated systemic ammonia levels, which may worsen hepatic encephalopathy [6].

Numerous studies have linked H. pylori infection to increased blood ammonia levels and a higher incidence of overt hepatic encephalopathy events in

patients with cirrhosis. The rapid uptake of ammonia from the gastric lumen to the bloodstream in H. pylori-infected patients indicates a potential etiological role for the bacterium in the pathogenesis of MHE. Despite evidence supporting the etiological role of hyperammonemia in HE, limited research has investigated the direct influence of H. pylori infection on the development and progression of MHE. Addressing this information gap is essential due to the negative impact of MHE on quality of life, cognitive function, daily activities, and the increased risk of developing overt HE.

H. pylori infection has been shown to exacerbate ammonia levels; thus, eradicating the infection may provide therapeutic benefits for patients with MHE. Prior studies indicate that the eradication of H. pylori results in decreased circulating ammonia levels and a reduction in symptoms associated with hepatic encephalopathy [7]. This indicates that targeted therapy for H. pylori infection may serve as a supplementary approach in the management of minimal hepatic encephalopathy in patients with cirrhosis. Further research is necessary to establish a definitive relationship between H. pylori infection and MHE, as well as to assess the effectiveness of anti-H. pylori treatment in enhancing neurocognitive function [8].

The influence of MHE extends beyond the individual patient, affecting public health and safety as well. Patients with MHE demonstrate impairments in reaction time, coordination, and attention, which significantly affect their capacity to perform daily activities, such as driving and operating vehicles. Research indicates that patients with MHE exhibit an increased risk of motor vehicle accidents due to delayed cognitive processing and impaired visuomotor coordination. MHE is linked to an increased risk of hospitalization and falls, contributing to a greater disease burden [9,10].

The pathophysiology of MHE is complex and multifactorial, primarily characterized by hyperammonemia. Additional processes, including neuroinflammation, dysfunction of neurotransmitters, and imbalance in gut microbiota, have also played a role in the pathogenesis of MHE. The gut-liver-brain axis is crucial for maintaining neurological homeostasis, and disruptions in this axis, such as those caused by H. pylori infection, can lead to neurocognitive impairment. Recent evidence supports the idea that gut dysbiosis, along with an imbalance between healthy and pathogenic gut microbiota, may exacerbate the severity of MHE. H. pylori serve as a crucial regulator of gastric and intestinal microbiota, potentially influencing pathophysiological events and actively contributing to the progression and development of MHE.

This study seeks to assess the prevalence of MHE in cirrhotic patients and investigate the relationship between Helicobacter pylori infection and hyperammonemia in this population. This study examines the impact of H. pylori eradication on blood ammonia levels and neuro psychometric performance, emphasizing the therapeutic potential of antimicrobial treatment in MHE. This study aims to contribute data on the pathophysiological mechanisms of MHE and offer targeted recommendations to enhance patient outcomes. The identification of H. pylori's role in the pathogenesis of MHE may lead to novel therapeutic strategies aimed at enhancing cognitive function and quality of life in patients with cirrhosis."

Methodology

Study Design: This was a prospective observational study designed to assess the impact of Helicobacter pylori (H. pylori) infection on the etiology of minimal hepatic encephalopathy (MHE) and the effects of eradication.

Study Area: The study was conducted at Department of Gastroenterology, S.M.S. Medical college, Jaipur, Rajasthan, India, with a dedicated hepatology and gastroenterology unit, providing diagnostic and therapeutic services to patients with liver diseases.

Study Duration: The study was conducted over a period of 1 year from January 2013 to December 2013

Sample Size: Out of 190 patients with liver cirrhosis initially screened for the study, only 75 met the criteria and were included in the final analysis.

Sample Collection: Patients with probable cirrhosis underwent ultrasonography and endoscopic evaluations. The study comprised individuals diagnosed with chronic liver disease and esophageal varices. At baseline, biochemical and psychometric assessments were conducted, and antral samples were collected during endoscopy for H. pylori identification with the fast urease test.

Inclusion Criteria

- Patients exhibiting ultrasonographic indications of chronic liver disease.
- Identification of esophageal varices during endoscopic evaluation.
- Patients who grant written informed consent.

Exclusion Criteria

- A recent history of bleeding in the upper gastrointestinal tract.
- A clinical examination reveals the existence of overt hepatic encephalopathy.
- Individuals with vision impairment or neurological conditions that may impact psychometric testing.
- Treatment history for H. pylori eradication throughout the previous three months.

Procedure

"At baseline, all patients received standard hematological and biochemical assessments, which included HBsAg, anti-HCV testing, and ultrasonography. Ascitic fluid, if present, was subjected to analysis. Plasma ammonia levels were assessed utilizing the Menagent Ammonia Test Kit II. Upper gastrointestinal endoscopy was conducted, and a rapid urease test (Delta West, Bentley, Australia) was performed on an antral biopsy to identify H. pylori infection.

Psychometric assessments comprised the Number Connection Test (NCT), Figure Connection Test (FCT), and Line Tracing Test. Prior to the actual tests, patients received demonstrations, and a practice run to acclimate them to the procedures. The duration and error count were documented, and normative data were derived from 200 healthy control participants.

Patients diagnosed with minimal hepatic encephalopathy (MHE), regardless of their Helicobacter pylori status, were administered two weeks triple therapy regimen that included Amoxycillin (1g twice daily), Clarithromycin (500 mg twice daily) and Omeprazole (20 mg twice daily). Fasting blood ammonia levels and psychometric tests were re-evaluated four weeks post-treatment completion. Furthermore, patients who initially tested positive for H. pylori underwent a subsequent stool antigen test to verify eradication".

Statistical Analysis: "The data were presented as the means along with the standard deviation. The Chi-square test was utilized for the analysis of categorical variables, whereas the student's t-test was applied to compare continuous variables. A p-value of <0.05 was deemed statistically significant, suggesting a noteworthy difference between the groups being compared."

Result

Table 1 highlights the psychometric test results from 190 healthy participants, emphasizing the duration required for test completion and the associated higher cut-off values. The Number Connection Test was completed within 38 to 64 seconds, with a maximum threshold of 60 seconds. The Figure Connection Test exhibited completion durations between 64 and 98 seconds, with a maximum threshold established at 90 seconds. The Line Tracing Test was ultimately performed within 20 to 40 seconds, with the maximum threshold established at 40 seconds. These threshold values are utilized to evaluate standard test efficacy.

Table 1: Psychometric test findings in 190 healthy people and cut-offs based on them

Test	Time taken for test completion (sec)	Upper cut-off value (sec)
Line tracing test	20–40	40
Figure connection test	64–98	90
Number connection test	38–64	60

Table 2 shows the demographic and clinical attributes of the study participants. Out of 190 screened individuals, 75 were included, comprising 40 with Minimal Hepatic Encephalopathy (MHE) and 35 without (NMHE). The male-to-female ratio was 138:52 among screened patients and 58:17 among enrolled individuals. The average age of the groups was comparable, varying from 35.4 to 37.2 years. The etiology was diverse, with "Others" as the predominant cause (47 screened, 32 enrolled), followed by Hepatitis B virus (59 screened, 8 enrolled) and Alcohol (38 screened, 15 enrolled). Varices were identified in 149 screened individuals and 40 enrolled patients, comprising 22 in the MHE group and 18 in the NMHE group. The Child–Pugh classification indicated that the majority of enrolled patients were in class B (42 total, comprising 22 with Minimal Hepatic Encephalopathy (MHE) and 21 without (NMHE)), followed by class A (20 total) and class C (13 total).

Table 2: Study participants' demographic and clinical traits

Characteristic	Patients screened (n=190)	Patients enrolled (n=75)	MHE (n=40)	NMHE (n=35)
Male: Female	138: 52	58: 17	28: 12	30: 5
Mean age (years)	37.2	35.8	35.9	35.4
Etiology				
Others	47	32	17	15
Alcohol + Hepatitis B	16	11	6	5
Hepatitis C virus	30	9	4	5
Hepatitis B virus	59	8	5	3
Alcohol	38	15	8	7
Varices				
No	41	35	18	17

Yes	149	40	22	18
Child–Pugh class				
A	33	20	9	10
B	100	42	22	21
C	57	13	9	4

Table 3 presents a comparison of fasting blood ammonia levels before and after treatment in patients with minimal hepatic encephalopathy (MHE), categorized by H. pylori status (positive and negative). In H. pylori–negative patients (n=15), the mean pre-treatment blood ammonia level was 1.38 ± 0.15 µg/mL, decreasing to 1.15 ± 0.17 µg/mL post-treatment. In patients positive for H. pylori (n=25), the pre-treatment level was 1.82 ± 0.30 µg/mL, which significantly decreased to 1.20 ± 0.25 µg/mL following treatment. This indicates that treatment significantly reduced ammonia levels, particularly in H. pylori–positive patients.

Table 3: Fasting blood ammonia levels before and after treatment in H. pylori– negative and H. pylori–positive patients with minimal hepatic encephalopathy

H. pylori status	Blood ammonia levels (µ\muµg/mL)	
	Pre-treatment	**Post-treatment**
Negative (n=15)	1.38 (0.15)	1.15 (0.17)
Positive (n=25)	1.82 (0.30)	1.20 (0.25)

Table 4 displays the psychometric test outcomes prior to and following management for H. pylori infection in patients diagnosed with minimal hepatic encephalopathy (MHE). The Line Tracing Test indicated a decrease in completion time from 47 ± 12 seconds before treatment to 39 ± 11 seconds after treatment ($p < 0.001$). In a similar manner, the Figure Connection Test time was reduced from 126 ± 20 seconds to 109 ± 21 seconds ($p < 0.001$), and the Number Connection Test time showed improvement from 85 ± 14 seconds to 74 ± 15 seconds ($p < 0.001$). The notable enhancements indicate that H. pylori treatment has a beneficial effect on cognitive function in patients with MHE.

Table 4: Psychometric test results prior to and following treatment for H. pylori infection in patients exhibiting minimal hepatic encephalopathy

Psychometric test	Pre-treatment (sec)	Post-treatment (sec)	p value
Line tracing test	47 (12)	39 (11)	< 0.001
Figure connection test	126 (20)	109 (21)	< 0.001
Number connection test	85 (14)	74 (15)	< 0.001

Discussion

The research established baseline psychometric performance in healthy individuals, which is crucial for identifying minimal hepatic encephalopathy (MHE). In healthy participants, the number connection test was completed in 38–64 seconds (upper cut-off at 60 seconds), the figure connection test in 64–98 seconds (cut-off at 90 seconds), and the line tracing test in 20–40 seconds (cut-off at 40 seconds). These values functioned as benchmarks for evaluating cognitive impairment in individuals with liver disease.

"A number of studies have investigated the association between Helicobacter pylori (H. pylori) infection and minimal hepatic encephalopathy (MHE), yielding insights that both support and contradict our findings. A study conducted by Bajaj et al. (2010) [11] examined the persistence of cognitive impairment after the resolution of overt hepatic encephalopathy (OHE). The study indicates that occurrences of OHE correlate with enduring and cumulative impairments in working memory, response inhibition, and learning capabilities. This study emphasizes the significance of cognitive assessments in patients with liver disease, which is pertinent to our baseline psychometric performance results in healthy individuals.

A study by Malaguarnera et al. (2014) [12] investigated the role of gut microbiota in alcoholic liver disease, addressing its pathogenetic implications and potential therapeutic approaches. The authors emphasized that both qualitative (dysbiosis) and quantitative (bacterial overgrowth) changes in the intestinal microbiome contribute to elevated endotoxin levels, resulting in liver damage. This study indicates that factors including liver disease severity, nutritional status, and additional comorbidities may affect psychometric outcomes, underscoring the necessity of establishing stringent baseline performance parameters as demonstrated in our research."

The study population's demographic and clinical characteristics indicated that of the 190 patients screened, 75 were enrolled, comprising 40

diagnosed with MHE and 35 classified as non-MHE (NMHE). The average age among all groups was comparable, approximately 35 to 37 years. The gender distribution revealed a male predominance, especially within the NMHE group (30 males versus 5 females) in contrast to the MHE group (28 males versus 12 females). The etiological distribution was diverse, with cases linked to hepatitis B, hepatitis C, alcohol-related liver disease, and various combinations of these factors. A significant number of patients presented with varices and were categorized as Child–Pugh B or C, reflecting a more advanced stage of liver disease, especially in individuals with minimal hepatic encephalopathy (MHE).

"Agrawal et al. (2011) [13] conducted a study examining the prevalence of H. pylori infection in cirrhotic patients and its correlation with minimal hepatic encephalopathy (MHE). The prevalence of H. pylori infection was higher in patients with minimal hepatic encephalopathy (MHE) at 63%, in contrast to 37% in those without MHE. Moreover, eradication therapy resulted in a notable decrease in blood ammonia levels and enhancements in psychometric test outcomes, indicating a positive impact of H. pylori eradication on minimal hepatic encephalopathy (MHE).

A study conducted in Egypt by Amer et al. (2018) assessed the impact of H. pylori eradication on minimal hepatic encephalopathy in cirrhotic patients. The study found that 63.3% of patients with minimal hepatic encephalopathy (MHE) tested positive for H. pylori, in contrast to 40% in the non-MHE cohort. Following post-eradication therapy, patients with minimal hepatic encephalopathy (MHE) demonstrated notable enhancements in number connection test scores and a reduction in serum ammonia levels, underscoring the potential significance of H. pylori eradication in the management of MHE.

In contrast, Schulz et al. (2016) [15] conducted a study to assess the prevalence of H. pylori infection in patients with minimal hepatic encephalopathy (MHE) and its impact on blood ammonia levels. It was reported that 22% of patients infected with H. pylori exhibited minimal hepatic encephalopathy (MHE), whereas 30% of H. pylori-negative patients also presented with MHE. Furthermore, merely 19% of patients with minimal hepatic encephalopathy exhibited elevated blood ammonia levels. The research findings indicate that H. pylori infection does not have a significant effect on venous ammonia levels, and that eradication therapy may not offer further advantages in the management of hepatic encephalopathy in patients with cirrhosis.

The difference between the fasting blood ammonia levels of MHE patients with H. pylori-positive and H. pylori-negative bacteria before and after treatment was a noteworthy finding. Pre-treatment ammonia concentrations in H. pylori–positive patients were significantly elevated (1.82 ± 0.30 μg/mL) relative to H. pylori–negative patients (1.38 ± 0.15 μg/mL). After H. pylori eradication therapy, ammonia levels in the positive group significantly decreased to 1.20 ± 0.25 μg/mL, whereas the negative group exhibited only a minor reduction to 1.15 ± 0.17 μg/mL. This indicates that H. pylori infection may play a role in increasing ammonia levels, which are recognized as a contributing factor in the pathogenesis of MHE.

Abdel-Hady et al. (2007) [16] conducted a study examining the association between H. pylori infection, plasma endotoxins, and blood ammonia levels in individuals with hepatic encephalopathy. H. pylori infection was observed to be more prevalent in patients with hepatic encephalopathy (58%) than in non-cirrhotic controls (30%). Additionally, patients with cirrhosis who tested positive for H. pylori demonstrated markedly elevated fasting arterial blood ammonia and plasma endotoxin levels compared to those who were negative for H. pylori. The eradication of H. pylori resulted in a notable reduction in ammonia levels and the severity of hepatic encephalopathy, indicating a potential role of H. pylori in hyperammonemia and endotoxemia linked to hepatic encephalopathy."

In contrast, certain studies have raised doubts regarding the influence of H. pylori infection on ammonia levels and hepatic encephalopathy. A review by DUSEJA et al. [17] indicated that although H. pylori generate ammonia, the quantity may be inadequate to substantially influence hepatic encephalopathy. They acknowledged that eradication therapy has been demonstrated to enhance blood ammonia levels and hepatic encephalopathy in specific instances, suggesting that the impact of H. pylori may differ among individuals.

"Additional evidence of enhancement in psychometric test performance was observed after the eradication of H. pylori. In patients with MHE, the line tracing test time decreased from 47 ± 12 seconds before treatment to 39 ± 11 seconds after treatment. The figure connection test time decreased from 126 ± 20 seconds to 109 ± 21 seconds, while the number connection test time improved from 85 ± 14 seconds to 74 ± 15 seconds. The observed improvements were statistically significant ($p < 0.001$), suggesting that the eradication of H. pylori correlates with enhanced cognitive function as assessed by these standardized tests.

A study by Salem et al. [18] similarly assessed the effects of H. pylori eradication on patients with minimal hepatic encephalopathy (MHE).

Significant improvements in psychometric test scores, including the NCT, were observed following eradication therapy. The observed improvement coincided with a decrease in serum ammonia levels, highlighting the potential involvement of H. pylori in hyperammonemia and cognitive impairment among cirrhotic patients.

A study by Abid et al. (2020) [19] found no significant difference in blood ammonia levels between H. pylori-positive and -negative cirrhotic patients. Additionally, it was reported that the eradication of H. pylori did not result in notable enhancements in psychometric or electrophysiological test outcomes utilized for diagnosing MHE. The findings indicate that H. pylori infection may not significantly contribute to the pathogenesis of MHE, and its eradication may not provide cognitive benefits in patients with cirrhosis.

The findings underscore the potential involvement of H. pylori infection in the advancement of MHE. The correlation between elevated ammonia levels and cognitive impairment in infected individuals indicates that the bacterium may play a role in exacerbating the condition. The notable reduction in ammonia levels and enhancement in psychometric performance after H. pylori eradication indicates that addressing this infection may serve as an effective therapeutic strategy for managing minimal hepatic encephalopathy in individuals with liver disease."

Conclusion

The study examine that *Helicobacter pylori* infection seems to facilitate the onset of mild hepatic encephalopathy by negatively impacting cognitive abilities and metabolic factors. Patients with the infection demonstrated diminished performance on psychometric assessments and elevated blood ammonia levels, indicating compromised neurocognitive functioning. The elimination of H. pylori resulted in significant enhancements in psychometric performance and biochemical indicators, indicating that addressing the infection may alleviate certain neurocognitive deficits linked to mild hepatic encephalopathy.

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