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Role of Helicobacter Pylori Infection in the Pathogenesis of Minimal Hepatic Encephalopathy and Effect of its Eradication

Authors
Perihan El Sayed Salem[1], Fathalla Sidkey Mohamed[1], Dalia Abd El Moaty El Niely[2], Tamer Mohamed Yousri Balbaa[1]
[1]Internal Medicine Department, Faculty of Medicine, Alexandria University
[2]Clinical and Chemical Pathology Department, Faculty of Medicine, Alexandria University
Corresponding Author
Perihan El Sayed Salem
Assistant Professor of Internal Medicine, Faculty of Medicine, Alexandria University
Telephone: +2 01001815239 / +2 03 5828867
Email: *drperihansalem@yahoo.com,Fax: +2 03 5445454*

Abstract
Background and purpose *Minimal hepatic encephalopathy (MHE) is the mildest form in the spectrum of hepatic encephalopathy (HE); it has no recognizable clinical symptoms but mild cognitive and psychomotor deficits. Neuropsychometric testing is an established methodology for quantifying cognitive impairment in MHE. Ammonia is important in the pathogenesis of MHE and H. pylori are known to produce copious amounts of ammonia, thus, it may contribute to the development of MHE in the presence of liver cirrhosis. The study aimed to detect the prevalence of H. pylori infection in cirrhotic patients with and without MHE and to establish the correlation between the presence of H. pylori infection and blood ammonia level and the results of neuropsychometric tests in these cases. Moreover, to investigate the effect of H. pylori eradication on different measured parameters.*
Material and Methods *80 patients with HCV related liver cirrhosis were included in the study; patients were divided according to the presence or absence of MHE and H. pylori infection into 4 subgroups. Full history taking, routine laboratory investigations, fasting blood ammonia level and detection of H. pylori antigen in stool were done to all studied patients. Also, neuropsychometric tests were performed for diagnosis of MHE.*
Results and conclusion *H. pylori infection is common among cirrhotic Egyptian patients and its role in the pathogenesis of MHE and ammonia production was proved. Screening of cirrhotic patients for detection and eradication of H. pylori is beneficial in the improvement and cure of MHE for better quality of life.*
Keywords *Liver cirrhosis, Minimal hepatic encephalopathy, H. pylori infection, serum ammonia level, Neuropsychometric tests, H. pylori eradication.*

Introduction

Minimal hepatic encephalopathy (MHE) is the mildest form in the spectrum of hepatic encephalopathy (HE) with high incidence in cirrhotic patients and evidences suggest that its pathogenesis is similar to that of overt HE (OHE) where ammonia is considered to play a key role.[1]

MHE has no recognizable clinical symptoms, but it has mild cognitive and psychomotor deficits, together with decreased attention and working performance with poor memory that impair quality of life.[2] For its diagnosis, neuropsychometric tests, neurophysiologic tests (electroencephalography, P300 evoked potentials), computerized tests (critical flicker frequency test, inhibitory control test) or their combinations are used.[3]

Neuropsychometric tests are considered as an established methodology for quantifying cognitive impairment in MHE, they include number connection test (NCT),[4] figure connection test (FCT),[5] and line tracing test (LTT).[6]

Helicobacter pylorus (H. pylori) is considered a major health threat, in Egypt; a recent study demonstrated that the seroprevalence of H. pylori increased significantly in patients with cirrhosis.[7] H. pylori known to produce copious amounts of ammonia due to its strong urease activity, thus H. pylori infection may potentially contribute to the development of MHE in the presence of liver cirrhosis.[8]

Aim of work

The present study aimed to detect the prevalence of H. pylori infection in HCV related cirrhotic patients with and without minimal hepatic encephalopathy (MHE), and to establish the correlation between the presence of H. pylori infection and blood ammonia level and neuropsychometric tests in these patients. Also, to investigate the effect of H. pylori eradication on blood ammonia level and MHE in such patients.

Subjects

The study included 80 patients with HCV related liver cirrhosis who were admitted to Hepatobiliary Unit, Internal Medicine Department, Alexandria Main University Hospital. Patients were divided into 2 groups:-

Group (I): 40 patients with documented liver cirrhosis and MHE. Liver cirrhosis was diagnosed by laboratory and imaging tests and MHE was diagnosed by neuropsychometric tests. These patients were subdivided into 2 subgroups:

Group (IA): included patients (n=21) with documented H. pylori infection by fecal antigen test. These patients were assessed before and 4 weeks after receiving anti-H. pylori therapy.

Group (IB): included patients (n=19) without H. pylori infection.

Group (II): 40 patients with documented liver cirrhosis without MHE. These patients were subdivided into 2 subgroups:

Group (IIC): included patients (n=32) without H. pylori infection.

Group (IID): included patients (n=8) with H. pylori infection.

We excluded patients with history of recent upper gastrointestinal bleeding, OHE (based on clinical examination), neurological illness, poor vision, and H. pylori treatment within the previous three months.

Methods

All patients were subjected to the following:

1- Full history taking with particular stress on the exclusion criteria.
2- Complete clinical examination (general and local) including signs and symptoms of chronic liver disease, tests for ascites together with liver & spleen examination.
3- Laboratory investigations, including: complete blood count, liver test profile (ALT; AST; total serum bilirubin; prothrombin time; serum albumin), hepatitis virus markers (anti-HCV antibodies, HBsAg), fasting venous

ammonia level, detection of H. pylori antigen in stool.

4- Neuropsychometric tests; including:
   - Number connection test (NCT): in which circles include numbers from 1-13 and letters from A-L. The subjects were asked to connect numbers and letters in alternating manner, that means go from 1-A-2-B-3-C and so on. Test result is the time needed to end the test; the normal time taken for test completion is 39-65 seconds.[4]
   - Figure connection test (FCT): it includes five main circles that have figures inside; each main circle has another four circles with figures that are related to the main one. The subjects were asked to connect each main circle with its related one; the time taken to end this test is the result. The normal time taken for test completion is 65-99 seconds.[5]
   - Line tracing test (LTT): the subjects have to follow the route of this labyrinth without crossing or even touching the borderlines. The time needed to go through the labyrinth is the test result. The reference normal time is 75 seconds.[6]

   Before the actual tests, the procedure was explained and demonstrated. Time taken for completion of each test was recorded. Patients with abnormal results in two or more psychometric tests will be taken as having MHE.

5- Follow up for patients with documented H. pylori infection and MHE (**Group IA**) who received triple anti- H. pylori therapy (clarithromycin 500 mg, omeprazole 20 mg and tinidazole 500 mg each twice daily for one week) was done, where H. pylori stool antigen; fasting blood ammonia level and psychometric tests were repeated four weeks later. H. pylori positive patients who did not respond to the triple anti- H. pylori therapy were given another one week treatment.

6- All subjects included in the study signed an informed written consent before joining the study.

Results

Table (1) showed different studied groups regarding demographic data.

In our study, fatigue; anorexia and weight loss were common findings in the studied cirrhotic patients regardless the presence or absence of MHE and H. pylori infection. Other findings as jaundice; palmer erythema; lower limb edema; splenomegaly and ascites were also reported with variable percentages.

As regards Child-Pugh classification, most of the studied cirrhotic patients were child A (90.5%, 68.4%, 84.4% and 87.5% in **Groups IA**, **IB**, **IIC** and **IID** respectively). Child B was reported in 9.5%, 26.3%, 12.5% and 12.5% of **Groups IA**, **IB**, **IIC** and **IID** respectively. Only two patients were child C, where one belonged to **Group IB** and the other to **Group IIC**.

In the present study, the prevalence of H. pylori infection was 36.25% among studied cirrhotic patients (n=80) regardless the presence or absence of MHE. However, the prevalence was 52.5% and 20% in those with and without MHE respectively.

Anemia and thrombocytopenia were reported among large number of the studied cirrhotic patients regardless the presence or absence of MHE and H. pylori infection. On the other hand, white blood cells count showed an average median among different studied groups.

As regards ALT, AST, total serum bilirubin and serum albumin levels, they showed close median values among studied patients, with no statistically significant difference among different groups.

Table (2) showed comparison between different studied groups according to serum ammonia level

and neuropsychometric tests. As regards serum ammonia level, it showed a mean of 82.9±45.54 mcg/dl, 54.05±41.49 mcg/dl, 36.66±20.87 mcg/dl and 43.88±31.0 mcg/dl in **Groups IA**, **IB**, **IIC** and **IID** respectively. It was clear that most of the abnormal high results were in **Groups IA, IB** and **IID**, where more than half of **Group IA** patients with MHE and H. pylori infection (52.4%) showed abnormal high serum ammonia level while, only 21.1% and 12.5% of **Groups IB** and **IID** showed abnormal high serum ammonia level. None of **Group IIC** patients with neither H. pylori infection nor MHE had abnormal high serum ammonia level. A statistical significant difference was reported between **Group IA** and **IB**, where the median of serum ammonia level was 80 mcg/dl and 53 mcg/dl respectively. Again, a statistical significant difference was reported between Group **IIC** and **IID**, where the median of serum ammonia level was 34 mcg/dl and 42 mcg/dl respectively.

NCT showed a mean of 94.10±20.06 seconds, 90.47±25.41 seconds, 51.66±7.07 seconds and 54.13±9.33 seconds in **Groups IA**, **IB**, **IIC** and **IID** respectively. A statistical significant difference was reported between **Group I** and **II** as 33 patients in **Group I** had abnormal results while only one patient had abnormal results in **Group II.**

FCT showed a mean of 124.52±15.64 seconds, 119.05±22.77 seconds, 83.69±10.07 seconds and 79.13±15.83 seconds in **Groups IA**, **IB**, **IIC** and **IID** respectively. A statistical significant difference was reported between **Group I** and **II** as 36 patients in **Group I** had abnormal results while only one patient had abnormal results in **Group II.**

As regards LTT, it showed a mean of 77.62±21.44 seconds, 79.32±19.07 seconds, 59.12±20.14 seconds and 55.63±17.49 seconds in **Groups IA**, **IB**, **IIC** and **IID** respectively. No significant difference was reported among different studied groups.

Table (3) showed serum ammonia level and results of neuropsychometric tests in **Group IA** patients with MHE and H. pylori infection before and after treatment with triple anti- H. pylori therapy. As regards serum ammonia, its mean level was 82.90±45.54mcg/dl and 39.52±19.47 mcg/dl before and after treatment respectively with significant decrease in its level after treatment (P<0.001).

Also, the mean of NCT time was 94.10±20.06 seconds and 53.86±9.39 seconds before and after treatment respectively, with a statistical significant difference between both categories (P<0.001). Only one patient had abnormal prolonged time of NCT after treatment. The mean of FCT time was 124.52±15.64 seconds and 89.86±8.48 seconds before and after treatment respectively, with a statistical significant difference between both categories (P<0.001). Again, only one patient had abnormal prolonged time of FCT after treatment. Moreover, the mean of LTT time was 77.62±21.44 seconds and 50.19±12.37 seconds before and after treatment respectively, with a statistical significant difference between both categories (P<0.001). Also, only one patient had abnormal prolonged time of LTT after treatment. Thus, the majority of the treated patients in this group showed significant improvement in the results of neuropsychometric tests with cure of MHE in response to H. pylori eradication.

Table (1): Comparison between the different studied groups regarding demographic data.

	Group I				Group II				Test of sig.	p
	A (n=21)		B (n=19)		C (n=32)		D (n=8)			
	No	%	No	%	No	%	No	%		
Sex										
Male	20	95.2	19	100.0	31	96.9	8	100.0	X^2= 1.184	^{MC}p=1.000
Female	1	4.8	0	0.0	1	3.1	0	0.0		
Age										
Mean ± SD.	53.57±8.15		50.79±8.05		51.03±9.06		51.50±5.98			
Median	50.0		50.0		53.0		50.50			

x^2: value for Chi square MC: Monte Carlo test F: F test (ANOVA)

Table (2): Comparison between the different studied groups regarding serum ammonia level and neuropsychometric tests.

	Group I				Group II				Test of sig.	p
	A (n=21)		B (n=19)		C (n=32)		D (n=8)			
	No	%	No	%	No	%	No	%		
Ammonia (mcg/dl)										
Normal	10	47.6	15	78.9	32	100.0	7	87.5	□□= 22.056*	$^{MC}p<0.001$*
Abnormal	11	52.4	4	21.1	0	0.0	1	12.5		
Mean ± SD.	82.90±45.54		54.05±41.49		36.66±20.87		43.88±31.0			
Median	80.0		53.0		34.0		42.0			
NCT (seconds)										
Normal	2	9.5	5	26.3	31	96.9	8	100.0	□□= 53.555	$^{MC}p<0.001$*
Abnormal	19	90.5	14	73.7	1	3.1	0	0.0		
Mean ± SD.	94.10±20.06		90.47± 25.41		51.66 ± 7.07		54.13 ± 9.33			
Median	92.0		90.0		50.50		57.50			
FCT (seconds)										
Normal	1	4.8	3	15.8	31	96.9	8	100.0	□□= 62.110*	$^{MC}p<0.001$*
Abnormal	20	95.2	16	84.2	1	3.1	0	0.0		
Mean ± SD.	124.52±15.64		119.05±22.77		83.69±10.07		79.13±15.83			
Median	127.0		115.0		85.0		85.50			

LTT (seconds)										
Normal	9	42.9	9	47.4	26	81.25	7	87.5	□□= 12.366*	MCp=0.006
Abnormal	12	57.1	10	52.6	6	18.75	1	12.5		
Mean ± SD.	77.62±21.44		79.32±19.07		59.12±20.14		55.63±17.49			
Median	79.0		80.0		54.0		49.50			

□□: value for Chi square MC: Monte Carlo test FF test (ANOVA)
KW□□: Chi square for Kruskal Wallis test #Sig. bet. grps was done using Chi square or Fisher Exact test
@Sig. bet. grps was done using Post Hoc Test (Scheffe)
*: Statistically significant at p ≤ 0.05
: Statistically significant at p ≤ 0.01 *: Statistically significant at p ≤ 0.001

Table (3): Serum ammonia level and duration of neuropsychometric tests in Group IA patients before and after treatment with triple anti H. pylori therapy.

	Before (n = 21)		After (n = 21)		Test of sig.	p
	No	%	No	%		
Ammonia (mcg/dl)						
Normal	10	47.6	21	100.0	□□=14.903*	<0.001*
Abnormal	11	52.4	0	0.0		
Mean ± SD.	82.90±45.54		39.52±19.47			
Median	80.0		43.0			
NCT (seconds)						
Normal	2	9.5	20	95.2	□□=30.927*	<0.001*
Abnormal	19	90.5	1	4.8		
Mean ± SD.	94.10±20.06		53.86±9.39			
Median	92.0		58.0			
FCT (seconds)						
Normal	1	4.8	20	95.2	□□=34.381*	<0.001*
Abnormal	20	95.2	1	4.8		
Mean ± SD.	124.52±15.64		89.86±8.48			
Median	127.0		93.0			
LTT (seconds)						
Normal	9	42.8	20	95.2	□□= 13.480*	FEp<0.001*
Abnormal	12	57.1	1	4.8		
Mean ± SD.	77.62±21.44		50.19±12.37			
Median	79.0		49.0			

□□: Chi square test FE: Fisher Exact test t: Paired t-test
Z: Z for Wilcoxon signed ranks test *: Statistically significant at p ≤ 0.05

Discussion

MHE in patients with liver cirrhosis is defined by the presence of unexplained cognitive abnormalities, only detectable on psychometric testing in the absence of OHE.[9] Ammonia is a key factor in the pathogenesis of OHE and MHE in cirrhotic patients, and therapeutic interventions of proven benefit in this setting, such as treatment with lactulose (4-O-β-d-galactopyranosyl-d-fructose), are generally aimed at reducing ammonia levels.[10]

H. pylori are rich in urease enzyme and known to produce ammonia from urea that is rapidly absorbed from gastric lumen into circulation. Infection with these bacteria has been shown to be associated with elevated blood ammonia level and recurrent attacks of OHE and MHE in cirrhotic patients.[11] Eradication of H. pylori infection has been shown to be associated with reduction in blood ammonia level and improvement in HE.[12]

The aim of the present study was to detect the prevalence of H. pylori infection in HCV related cirrhotic patients with and without MHE, and to establish the correlation between the presence of H. pylori infection and blood ammonia level and neuropsychometric tests in these patients. Also, to assess the effect of H. pylori eradication on blood ammonia level and MHE in such patients.

In the present study, males predominated females in all studied groups; this was in accordance with Nafee AM et al [13] where the reasons for the disparity between men and women may be genetic, hormonal and environmental factors such as higher prevalence of chronic HBV and HCV infection, alcohol abuse and smoking in men than in women.

As regards age, it ranged between 31-66 years which was in agreement with Rekha C et al [14] who investigated the role of H. pylori in 47cirrhotic patients with subclinical HE, this study showed that age ranged between 23-60 years.

In our study, fatigue; anorexia and weight loss were common findings in the studied cirrhotic patients which was in accordance with Kalaitzakis E et al.[15] Also, jaundice; palmer erythema; lower limb edema; splenomegaly and ascites were reported with variable percentages, Topdagi O et al [16] reported the same findings in their studied patients with liver cirrhosis. As regards Child-Pugh classification, most of the studied cirrhotic patients were child A which was in agreement with Rekha C et al [14] who stated that most of the studied patients were child A (48.9%), where 31.9% and 19.1% were child B and C respectively.

In the present study, the prevalence of H. pylori infection was 36.25% among studied cirrhotic patients (n=80) regardless the presence or absence of MHE. However, the prevalence was 52.5% and 20% in those with and without MHE respectively.

Our findings regarding CBC and liver function tests were in accordance with those reported by Rekha C et al,[14] Khoshnood A et al [17] and Wilkins T et al.[18]

As regards serum ammonia level, it showed a mean of 82.9±45.54 mcg/dl, 54.05±41.49 mcg/dl, 36.66±20.87 mcg/dl and 43.88±31.0 mcg/dl in **Groups IA**, **IB**, **IIC** and **IID** respectively. Our study revealed that patients with MHE **(Group I)** had higher serum ammonia levels than those without MHE **(Group II)**. Also, its level showed a statistically significant difference in **Group IA** (H. pylori positive) in comparison to **Group IB** (H. pylori negative) with P<0.001.

In agreement with our study, Agrawal A et al [19] found that serum ammonia level was significantly higher in patients with MHE than those without MHE (P<0.001). Also, among patients with MHE, serum ammonia level was significantly higher in H. pylori positive than negative patients (P<0.001). Also, El Ghonaimy SM et al [20] stated that the mean level of serum ammonia was significantly higher in H. pylori positive patients in comparison to H. pylori negative patients (P<0.001).

In disagreement with our study, Vasconez C et al [11] and Rekha C et al [14] reported that the mean level of serum ammonia in H. pylori negative patients was slightly higher than that in H. pylori positive patients.

As regards neuropsychometric tests, El Ghonaimy SM et al [20] were in agreement with our results where they stated that the time needed to perform NCT showed the lowest mean in H. pylori negative patients in comparison to H. pylori positive with a statistically significant difference (P<0.001). Also, Agrawal A et al [19] reported that the time needed to perform FCT showed a mean of 127±19 seconds in cirrhotic patients with MHE and positive H. pylori infection. However, different to our results, they reported that the time needed to perform LTT showed a mean of 48±13 seconds in cirrhotic patients with MHE and positive H. pylori infection.

In our study, a statistical significant decrease was observed in serum ammonia level and duration of neuropsychometric tests after anti- H. pylori triple therapy for **Group IA** patients with MHE and H. pylori infection. Thus, the majority of treated patients in this group showed significant cure of MHE in response to therapy.

In agreement with our study, Agrawal A et al [19] found that patients with MHE and H. pylori infection showed a significant reduction in blood ammonia levels and in the time taken to complete the psychometric tests after anti-H. pylori treatment (p<0.001).

Conclusion

H. pylori infection is common among HCV related cirrhotic Egyptian patients and its role in the pathogenesis of MHE and ammonia production was proved in several studies. Screening of cirrhotic patients for detection and eradication of H. pylori infection is beneficial in the improvement and cure of MHE with its cognitive abnormalities with better quality of life for these patients.

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