EFFECT OF HELICOBACTER PYLORI ERADICATIONON THE PATHOGENESIS OF MINIMAL HEPATIC ENCEPHALOPATHY IN EGYPTIAN PATIENTS WITH LIVER CIRRHOSIS

By

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Abstract

Hepatic encephalopathy is one of the complications of liver cirrhosis. Ammonia is implicated as a precipitating factor for HE, minimal hepatic encephalopathy cannot be detected clinically and impairs quality of life, indicated that *H. pylori* infection is associated with high blood ammonia levels by urease enzyme and can lead to causation of HE. This study evaluated the effect of *H. pylori* eradication therapy on MHE.

A total of 60 cirrhotic patients were selected from al-Hussein University Hospital. They were GI: 30 patients with MHE and GII; 30 patients without MHE.

All patients were subjected to *H. pylori* stool antigen and blood ammonia level. Positive *H. pylori* patients received triple therapy for 14 days, then 4 weeks later were revaluated regarding, *H. pylori* stool antigen, serum ammonia level and NCT. *Helicobacter pylori* infection was found 63.3% of GI versus 40% in GII; serum ammonia levels were significantly higher in patients with GI and *H. pylori* positive. Treatment was successful in 78.9% of GI patients versus 89.4% of GII. Number connection test and serum ammonia level were significantly improved in GI patients and positive *H. pylori* after eradication therapy.

Key words: Egypt, Minimal hepatic encephalopathy, Serum ammonia, *Helicobacter pylori*

Introduction

Hepatic Encephalopathy (HE) is a major complication that develops in a majority of patients with liver cirrhosis. Minimal hepatic encephalopathy (MHE), the mildest form of hepatic encephalopathy is characterized by subtle motor and cognitive deficits and impairs health related to the quality of life (Dhiman *et al,* 2010). The Minimal Hepatic Encephalopathy (MHE) is not detectable by clinical examination although it can be detected by sensitive tests of coordination like number connection test (NCT), figure connection test (FCT) and line tracing test, electro-encephalography and visual, audit-0ory and somatosensory evoked potentials (Agrawal *et al,* 2011)

Among different risk factors imply-cated in the pathogenesis of HE, hyperammonemia was found to be the most significant predictor of progression of MHE and it was widely concluded to be highly correlateed with MHE causation in both adult and pediatric populations (Foerster *et al,* 2009)

The epidemiology of *H. pylori* was very complex, different factors influencing the acquisition of *H. pylori* infection even within same geographic area (Dore and Vaira, 2003). The prevalence of infection is higher in developing countries (more than 80%) and lower in the developed ones (less than 40%) with a declining pattern world-wide (Azevedo *et al,* 2009). Valery *et al.* (2006) found that *H. pylori* were highly prevalent among socially and economically deprived children and poor hosing conditions were significantly associated to being infected.

Helicobacter pylori infection well known to be associated with development of precancerous lesions as chronic atrophic gastritis, or gastric intestinal metaplasia, and cancer (Watari et al, 2014). *H. pylori* bacteria are rich in urease enzyme that produces ammonia from urea rapidly absorbed from gastric lumen into circulation. Infection with these bacteria shown to be associated with eleva-

ted blood ammonia levels (Vilstrup *et al,* 2014) and urease causing a state of diminished gastric acidity, which favored giardiasis as well (David and William, 2006).

Patients and Methods

This study was carried out at Al-Azhar University Hospitals on 60 cirrhotic patients were divided in to two groups; GI: 30 MHE patients recognized by positive NCT. GII: 30 patients without MHE. Number connection test was a plain paper with randomly scattered number from 1-25 were connected in ascending manner within 45 seconds, any patient with NCT more than 45 second was diagnosed as MHE.

Any patient with history of proton pump inhibitors (PPI) use within last two weeks or presented with other causes of encephalopathy was excluded. The selected patients were subjected to written consent, full clinical evaluation, routine laboratory investigations and ultrasonography. Fecal *H. pylori* antigen and serum ammonia level were done before and four weeks post eradication therapy (Okuda *et al,* 2014).

Eradication treatment was levofloxacin 500mg/day, omeprazole 20mg twice daily and amoxicillin 1g twice daily for 14 days.

Compliance with Ethical Standards: All applicable international, national, and/or institutional guidelines for the care and treating patients were followed.

Results

In the present study, the patient groups did not differ regarding age and sex (Tab. 1).

Of 60 examined patients, only ten patients were child-B; six from MHE group and four from the Non-MHE, no Child-C was involved. No differences were detected between the groups as to clinical pictures, laboratory results and/or sonographic findings.

Serum ammonia level was significantly higher in MHE patients. *H. pylori* was detected in 19 patients (63.3%) and 12 (40%) of MHE and Non-MHE respectively. *H. pylori* were eradicated in 78.9% of MHE patients and 75% of Non-MHE with no significant differences in between (Tab. 2).

Significant drop in ammonia level after *H. pylori* treatment was seen among MHE and non-MHE groups. Eradication of therapy of *H. pylori* dramatically improved the MHE as NCT was improved in 89.4% of MHE patients (Tab. 3).

Table 1: Groups as regard age and sex.

Variable	MHE (n=30)	Non-MHE (n=30)	P value
Age	53.53±8.3	52.73±7.75	0.7 (NS)
Male /Female	12 /18	14/ 16	0.6 (NS)

Table 2: Serum ammonia level, positive *H. pylori* and successful triple therapy in groups

Items	MHE (n=30)	Non-MHE (n=30)	P value
S. ammonia	94.6±14.25	61.13 ±7.5	<0001 (S)
H. pylori +ve	19 (63.3%)	12 (40%)	0.07 (NS)
H. pylori successful therapy	15 (78.9%)	9 (75%)	0.68 (NS)

Table 3: Serum ammonia level andpositive NCT before and after triple therapy in *H. pylori*patients.

	MHE (n=19)		Non-MHE (n-12)	
	Before	After	Before	After
S. Ammonia	102.7 ± 10.36	80.25 ± 8.96*	65.92 ± 4.92	55.83 ± 4.83*
NCT +ve	19 (100%)	2 (10.5%)*	zero	

*significant

Discussion

Among the different risk factors implicated in the pathogenesis of the HE, hyperammonemia was found to be the commonest significant predictor of progression of MHE and it was widely concluded to be highly correlated with MHE causation in both adult and pediatric populations (Vilstrup *et al,* 2014). *H. pylori* is one of the main risk factors for HE in patients with liver cirrhosis (Yang *et al,* 2007). *H. pylori* has been suggested as possible source of ammonia production because of its high urease content (Zullo *et al,* 2003; 2015)

In the present study H. pylori infection had higher prevalence in MHE group (63.3%) compared to non-MHE group (40%). Although being statistically non-significant (p= 0.07), these findings agreed with Agrawal *et al.* (2011) who found that, the prevalence was 63% and 37 % in minimal and non-minimal hepatic encephalopathy groups respectively. Also, Saeed *et al.* (2014) reported that prevalence of H. pylori among the MHE and Non-MHE groups of patients was 61.7 and 55%, respectively (p < 0.05). Miquel *et al.* (2001) found that *H. pylori* infection occurred in 22/37 (59%) patients.

In the present study, among the MHE patients, 24 (80%) were classified as Child A and 6 (20%) as Child B, which agreed with Saeed *et al.* (2014) who reported that 58.3% of MHE patients were classified as Child B and Agrawal *et al.* (2011) who found that 23% MHE patients were Child's B.

The pre-treatment statistical evaluation of ammonia blood level was matched with the findings of NCT. Blood ammonia levels were significantly higher in MHE patients than non-MHE ones (p< 0.001), and ammonia levels were significantly higher in the MHE patients with positive *H. pylori* than in MHE patients negative for *H. pylori*, so strong association between *H. pylori* infection and MHE was noticed.

In the present study, both ammonia blood levels and number connection test scores are significantly higher in *H. pylori* positive cases compared to *H. pylori* negative ones distinct from the underlying hepatic status (Chen *et al,* 2008; Li *et al,* 2013)

In the present study, *H. pylori* infection was eradicated in 15/19 (78.94%) of MHE patients, this result agreed with Saeed *et al.* (2014) who found that *H. pylori* was eradicated in 29/37 (78.4%) of MHE patients.

In the present study, there was a significant reduction in blood ammonia levels in patients with or without MHE after triple therapy (p< 0.001). This reduction was more marked in MHE patients compared to non-MHE ones. Thus, *H. pylori* contributed to development of hyperammonemia in patients with liver disease and MHE. The role of *H. pylori* in the pathogenesis of hyperammonemia was peroved in previous studies which showed a reduction in blood ammonia levels after eradication of H. pylori infection (Chen *et al,* 2008; Agrawal *et al,* 2011). The reduction in blood ammonia levels following treatment with anti-H. pylori drugs was associated with resolution of MHE in 17 of our 19 patients with MHE and H. pylori infection with total percentage of resolution of 89.4% based on NCT score. Normalization of psychometric tests with reduction in blood ammonia levels has been reported previously, and further suggests a role of hyperammonemia in the pathogenesis of MHE (Schulz *et al,* 2014, Oeltzschner *et al,* 2015).

There were discrete reports indicating that ammonia level and/or number connection tests may not differ significantly in stable cirrhotic patients with *H. pylori* infection and hence eradication may be unnecessary (Scotiniotis *et al,* 2001; Kini *et al,* 2001; Hu *et al,* 2013). This discrepancy might be emphasized due to the obvious higher prevalence of H. pylori infection in these studies compared to other studies, different eradication regimens or intrinsic differences of the population under study.

Conclusion

Helicobacter pylori infection is significantly associated with minimal hepatic encephalopathy (MHE) and eradication treatment led to the reduction in ammonia level and improvement of MHE. Thus, the patients with chronic liver disease must be screened for *H. pylori* infection and properly treated.

References

Agrawal, A, Gupta, A, Chandra, M, Koowar, S, 2011: Role of Helicobacter pylori infection in the pathogenesis of minimal hepatic encephalopathy and effect of its eradication. Indian J. Gastroenterol. 30, 1:29-32.

Azevedo, NF, Huntington, J, Goodman, KJ, 2009: The epidemiology of *Helicobacter pylori* and public health implications. *Helicobacter* 14, 1:1-7.

Chen, SJ, Wang, LJ, Zhu, Q, Cai, JT, Chen, T, *et al,* **2008:** Effect of H pylori infection and its eradication on hyperammonemia and hepatic encephalopathy in cirrhotic patients. Wld. J. Gastroenterol. 14, 13:1914-8.

David, TJ; William, AP, 2006: Markell and Voge's Medical Parasitology. 9th edition; Saunders Elsevier, New York, USA,

Dhiman, RK, Saraswat, VA, Sharma, BK, Sarin, SK, Chawla, YK, *et al,* **2010:** Minimal hepatic encephalopathy: Consensus statement of a working party of the Indian National Association for Study of the Liver. J. Gastroenterol. Hepatol. 25, 6:1029-41.

Dore, MP, Vaira, D, 2003: Sheep rearing and *Helicobacter pylori* infection, an epidemiological model of anthropozoonosis. Dig. Liver Dis. 35, 1:7-9

Foerster, BR, Conklin, LS, Petrou, M, Barker, PB, Schwarz, KB, 2009: Minimal hepatic encephalopathy in children: evaluation with proton MR spectroscopy. Am. J. Neuroradiol. 30, 8: 34.

Hu, BL, Wang, HY, Yang, GY, 2013: Association of *Helicobacter pylori* infection with heaptic encephalopathy risk: A systematic review. Clin. Res. Hepatol. Gastroenterol. 37, 6:619-25.

Kini, D, Aggarwal, R, Saraswat, VA, Naik, S R, 2001: Role of *Helicobacter pylori* infection in hyperammonemia and subclinical hepatic encephalopathy in cirrhosis of liver, Indian J. Gastroenterol. 20, 6:237-40.

Li, SW, Wang, K, Yu, YQ, Wang, HB, Li, YH, *et al,* **2013:** Psychometric hepatic encephalopathy score for diagnosis of minimal hepatic encephalopathy in China. World J.Gastroenterol. 19, 46: 8745-51.

Miquel, J, Barcena, R, Boixeda, D, Fernandez, J, SanRoman, AL, *et al,* **2001:** Role of *Helicobacter pylori* infection and its eradication in patients with subclinical hepatic encephalopathy. Euro J. Gastroenterol. Hepatol. 13, 9:1067-72.

Oeltzschner, G, Butz, M, Baumgarten, TJ, Hoogenboom, N, Wittsack, HJ, *et al,* **2015:** Low visual cortex GABA levels in hepatic encephalopathy: links to blood ammonia, critical flicker frequency, and brain osmolytes. Metabol. Brain Dis. 30, 6:1429-38**.**

Okuda, M, Osaki, T, Kikuchi, S, Ueda, J, Lin, Y, *et al,* **2014:** Evaluation of a stool antigen test using a mAb for native catalase for diagnosis of *Helicobacter pylori* infection in children and adults. J. Med. Microbiol. 63:1621-5.

Saeed, HE, Musa, NI, Safwat, E, Mohamed, S M, Elbreedy, AM, 2014: *Helicobacter pylori,* hyperammonemia, and hepatic encephalopathy. Egypt. Liver J. 4, 3:75-8.

Schulz, C, Schütte, K, Malfertheiner, P, 2014: Does *H. pylori* eradication therapy benefit patients with hepatic encephalopathy? Systematic review. J. Clin. Gastroenterol. 48, 6:491-9.

Scotiniotis, IA, Lucey, MR, Metz, DC, 2001: *H. pylori* infection is not associated with subclinical hepatic encephalopathy in stable cirrhotic patients. Digest. Dis. Sci. 46, 12:2744-51.

Vilstrup, H, Amodio, P, Bajaj, J, Cordoba, J, Ferenci, P, *et al,* **2014:** Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the liver. Hepatol. 60:715-35.

Valery, MC, Barón, MA, Solano, L, Nadaff, G, Boccio, J, *et al,* **2006:** *Helicobacter pylori* infection (^{13}C-UBT), and its relationship with nutritional and socioeconomic factors in low income school children from Valencia, Venezuela. Arch. Latinoam. Nutr. 56, 4:342-9.

Watari, J, Chen, N, Amenta, PS, Fukui, H, Oshima, T, *et al,* **2014:** *Helicobacter pylori* associated chronic gastritis, clinical syndromes, precancerous lesions, and pathogenesis of gastric cancer development. World J. Gastroenterol. 20, 18:5461-73.

Yang, C, Cao, S, He, X, Wang, Y, Zhang, Y, 2007: Study of correlation between Helicobacter pylori infection and hyperammonemia and hepatic encephalopathy in cirrhotic patients. Zhongguoweizhong Chinese Crit. Care Med. 19, 7: 422-4.

Zullo, A, Hassan, C, Morini, S, 2003: *Helicobacter pylori* infection in patients with liver cirrhosis: facts and fictions. Dig. Liver Dis. 35, 3: 197-205.

Zullo, A, De Francesco, V, Hassan, C, Morini, S, Vaira, D, 2007: The sequential therapy regimen for *Helicobacter pylori* eradication: A pooled-data analysis. Gut 56, 10:1353-7.

Zullo, A, Ridola, L, De Francesco, V, Hassan, C, 2015: *Helicobacter pylori* eradication for hepatic encephalopathy treatment. J. Clin. Gastroenterol. 49, 1:88-9.