

# HELICOBACTER PYLORI AND THE INCIDENCE OF HEPATIC ENCEPHALOPATHY

By

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## ABSTRACT

**Background:** In the cirrhotic patients, the activity of Helicobacter Pylori (H Pylori) urease was believed as a source of gastric ammonia.

**Objective:** To evaluate the role of H pylori in pathogenesis of hepatic encephalopathy (HE).

**Patients and Methods:** This case control study was carried out on 100 patients, 18 years old or more and both sexes. Patients were divided into 3 groups; group A (n = 40): Liver cirrhosis (LC) (Child C) and positive H pylori, group B (n = 40): LC (Child C) and negative H pylori and group C (n = 20): Healthy persons as a control group. Stool H Pylori antigen, arterial blood ammonia and plasma endotoxins were done.

**Results:** Mean value  $\pm$  SD of serum ammonia was  $97.28 \pm 31.66$  ng/dL in group A,  $65.45 \pm 14.91$  ng/dL in group B and  $48.6 \pm 11.66$  ng/dL in group C. There was a significant increase in group A than B and C, and in group B than C. Mean value  $\pm$  SD of plasma endotoxin was  $0.55 \pm 0.11$  ng/dL in group A,  $0.34 \pm 0.12$  ng/dL in group B and  $0.25 \pm 0.09$  ng/dL in group C. There was a significant increase in group A than B and C, and in group B than C. HE significantly increased in group A (55.0%) than group B (17.5%).

**Conclusion:** Cirrhotic patients (Child C) with positive H pylori were associated with higher incidence of HE, higher levels of ammonia and endotoxins than patients with negative H pylori.

**Keywords:** Helicobacter Pylori - Hepatic encephalopathy - Serum ammonia - Plasma endotoxins.

## INTRODUCTION

Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome that occurs in severe liver failure patients (Ferenci, 2017).

The overall prevalence is not exactly known, but fifty to eighty percent of patients with liver cirrhosis (LC) have some cerebral dysfunction when

investigated by electroencephalography (EEG) or psychometric testing (Amodio & Montagnese, 2015). A multitude of factors and pathogenic processes appear to be operative, with the accumulation of toxic products in the brain, originating from the gut, not metabolized by the diseased liver, being the most important factor. The other mechanisms include abnormal neurotransmitter balance, changes in

cerebral metabolism, and changes in blood brain barrier permeability, impaired neuronal membrane sodium-potassium-ATPase activity, and abnormality in GABAergic neurotransmission (Ciećko-Michalska *et al.*, 2012).

In LC patients, plasma ammonia is thought to share in the pathogenesis of HE. The bacterial breakdown of urea and the metabolism of mucosal glutamines are the key sources of ammonia (Holecek, 2014, Rai *et al.*, 2015).

Although the primary source of ammonia is colonic bacteria, the stomach is a possible alternative source in subjects with urease generating *Helicobacter Pylori* (H Pylori). H pylori recognition as the cause of urease in the stomach has contributed to a re-emergence of concern about gastric urease and its products (Salama *et al.*, 2013 and Graham & Miftahussurur, 2018).

The aim of this work was to evaluate the role of H pylori in pathogenesis of HE.

## PATIENTS AND METHODS

This case control study was conducted on 100 patients, 18 years old or more and both sexes, referred for Internal Medicine Department, after approval of the Ethical and Medical Committee of Al-Hussein University Hospital and written informed consents from all participants.

### Patients were divided into 3 groups:

**Group A (n = 40):** Patients with LC (Child C) and positive H pylori.

**Group B (n = 40):** Patients with LC (Child C) and negative H pylori.

**Group C (n = 20):** Healthy persons, age and sex matched as a control group.

Exclusion criteria were history of recent bleeding, renal failure (creatinine > 3.0 mg/dL), history of antibiotic intake during the preceding four weeks, history of anti-H pylori therapy, history of any malignancy, and history of alcohol intake during the preceding three months.

### All patients were subjected to:

1. History taking (age, BMI, history of previous HE, DM, hypertension).
2. General and local examination.
3. Laboratory investigation: Complete blood count, liver function tests (ALT, AST, serum albumin, total serum bilirubin), INR, kidney function tests (serum creatinine, blood urea), electrolytes (serum sodium, serum potassium), stool Pylori Ag and detect genotype, arterial blood ammonia and plasma endotoxins.
4. Pelvi-abdominal US

Diagnosis of LC was relied on clinical, biochemical and radiological criteria.

### Statistical analysis:

Statistical analysis was done by SPSS v25 (IBM©, Chicago, IL, USA). Normality of data was checked by Shapiro-Wilks test and all data were normally distributed. Quantitative data were presented as range, mean and standard deviation (SD) and were compared by ANOVA (F) (with LSD post hoc test). Qualitative data were presented as number and percent and were compared by the Chi-square (X<sup>2</sup>). The level of significance was adopted at p<0.05.

RESULTS

There were insignificant differences as regards age, sex, BMI, DM and hypertension (Table 1).

Table (1): Patients characteristics of both groups

Groups		Group A (n = 40)	Group B (n = 40)	Group C (n = 20)	P value
Age (years)		54.325 ± 8.75	56.725 ± 9.78	54.3 ± 11.00	>0.05
Sex (n, %)	Male	24 (60.0%)	19 (47.5%)	13 (65.0%)	>0.05
	Female	16 (40.0%)	21 (52.5%)	7 (35.0%)	
BMI (Kg/m <sup>2</sup> )		28.68 ± 7.29	31.54 ± 6.64	31.53 ± 4.70	>0.05
Diseases (n, %)	D.M.	8 (20%)	12 (17%)	10 (50%)	>0.05
	Hypertension	4 (10%)	5 (7%)	3 (15%)	>0.05

BMI: body mass index, DM: diabetes mellitus

Hemoglobin, platelet count and albumin showed insignificant difference in group A than B. There was significant increase in group C than A and B. ALT, AST, TSB, INR, creatinine and urea

showed insignificant difference in group A than B, while there was significant decrease in group C than A and B. TLC, Na and K showed insignificant difference among the three groups (Table 2).

Table (2): Laboratory data of both groups

Groups		Group A (n = 40)	Group B (n = 40)	Group C (n = 20)	P value		
Hb (g/dL)	Range	8.5 - 13	9 - 13.5	10.5 - 14.4	<0.001*	P1	>0.05
	Mean ± SD	10.83 ± 1.40	11.30 ± 1.46	12.59 ± 1.20		P2	<0.001*
						P3	0.004*
Platelets (*10 <sup>3</sup> cells /mm <sup>3</sup> )	Range	69 - 306	67 - 303	163 - 382	<0.001*	P1	>0.05
	Mean ± SD	179.65 ± 75.68	209.1 ± 72.71	271.31 ± 76.13		P2	<0.001*
						P3	0.007*
TLC (*10 <sup>3</sup> cells /mm <sup>3</sup> )	Range	3.3 - 10.9	3.9 - 11.5	4.3 - 10.2	>0.05		
	Mean ± SD	7.19 ± 2.57	7.65 ± 2.29	7.08 ± 1.56			
ALT (U/L)	Range	21 - 82	21 - 78	20 - 42	<0.001*	P1	>0.05
	Mean ± SD	53.03 ± 19.19	46.83 ± 18.08	29.65 ± 7.27		P2	<0.001*
						P3	0.002*
AST (U/L)	Range	29 - 104	22 - 102	21 - 44	<0.001*	P1	>0.05
	Mean ± SD	68.53 ± 21.44	61.73 ± 18.84	32.15 ± 7.54		P2	<0.001*
						P3	<0.001*
TSB (mg/dL)	Range	0.8 - 4.1	0.7 - 4.1	0.5 - 1.2	<0.001*	P1	>0.05
	Mean ± SD	2.68 ± 1.09	2.31 ± 1.14	0.89 ± 0.20		P2	<0.001*
						P3	<0.001*
Albumin (g/dL)	Range	2.5 - 4	2.6 - 3.9	3.4 - 4.4	<0.001*	P1	>0.05
	Mean ± SD	3.225 ± 0.50	3.30 ± 0.39	3.97 ± 0.27		P2	<0.001*
						P3	<0.001*
INR	Range	1.1 - 2.8	1.2 - 2.9	1 - 1.5	<0.001*	P1	>0.05
	Mean ± SD	1.94 ± 0.57	2.09 ± 0.57	1.26 ± 0.14		P2	<0.001*
						P3	<0.001*

Creatinine (mg/dL)	Range	1.1 - 2.7	0.9 - 2.8	0.5 - 1.4	<0.001*	P1	>0.05
	Mean ± SD	1.94 ± 0.48	1.83 ± 0.55	0.92 ± 0.28		P2	<0.001*
						P3	<0.001*
Urea (mg/dL)	Range	60 - 149	60 - 150	25 - 45	<0.001*	P1	>0.05
	Mean ± SD	106.33 ± 26.50	99.57 ± 27.37	34.55 ± 6.11		P2	<0.001*
						P3	<0.001*
Serum sodium (mEq/L)	Range	129 - 145	130 - 145	135 - 146	>0.05		
	Mean ± SD	137.2 ± 4.67	137.6 ± 4.78	138.95 ± 2.91			
Serum potassium (mEq/L)	Range	2.9 - 5.5	2.8 - 5	3.6 - 4.6	>0.05		
	Mean ± SD	4.14 ± 0.78	3.98 ± 0.65	4.12 ± 0.31			

Hb: Hemoglobin, TLC: Total leucocytic count, ALT: Alanine Transferase, AST: Aspartate Transferase, TSB: Total serum bilirubin, INR: International normalized ratio \* significant as P value <0.05, P1: P value between group A and group B, P2: P value between group A and group C, P3: P value between group B and group C

Mean value ± SD of serum ammonia was 97.28 ± 31.66 ng/dL in group A, 65.45 ± 14.91 ng/dL in group B and 48.6 ± 11.66 ng/dL in group C. There was significant increase in group A than B and C and in group B than C (Table 3).

Mean value ± SD of plasma endotoxin was 0.55 ± 0.11 ng/dL in group A, 0.34 ± 0.12 ng/dL in group B and 0.25 ± 0.09 ng/dL in group C. There was significant increase in group A than B and C and in group B than C (Table 3).

**Table (3): Serum ammonia and plasma endotoxin levels of the patients**

Parameters		Group A (n = 40)	Group B (n = 40)	Group C (n = 20)	P value		
Ammonia	Range	47 - 149	33 - 90	30 - 67	<0.001*	P1	<0.001*
	Mean ± SD	97.28 ± 31.66	65.45 ± 14.91	48.6 ± 11.66		P2	<0.001*
						P3	0.025*
Endotoxin	Range	0.374 - 0.742	0.133 - 0.548	0.093 - 0.403	<0.001*	P1	<0.001*
	Mean ± SD	0.55 ± 0.11	0.34 ± 0.12	0.25 ± 0.09		P2	<0.001*
						P3	0.008*

P1: P value between group A and group B, P2: P value between group A and group C, P3: P value between group B and group C \* significant as P value <0.05

HE significantly increased in group A (22 patients (55.0%)) than group B (7 patients (17.5%)).

## DISCUSSION

LC is a chronic progressive liver disease that results in portal hypertension and liver cell failure. HE is characterized by neuropsychiatric manifestations in patients with liver dysfunction after exclusion of other brain diseases. It can be manifested by personality changes, intellectual impairment, and a depressed level of consciousness (Ellis & Mann, 2012).

In patients with HE, dysmetabolism of ammonia does not reveal all the neurological changes (El-Lehle *et al.*, 2019). Endotoxin, the lipopolysaccharide in the outer membrane of Gram-negative bacteria, enters the systemic circulation due to intestinal bacterial translocation and portosystemic shunting results in chronic endotoxemia (Bellot *et al.*, 2013). Circulating endotoxins from the gut cause sterile inflammation by releasing

proinflammatory mediators which directly signal to the brain (*Coltart et al., 2013*). H Pylori bacteria are rich in urease enzyme producing ammonia from gastric lumen into circulation, causing HE has observed that eradication of H pylori may reduce the concentration of ammonia in LC patients (*Perazzo et al., 2012*).

Serum ammonia significantly increased in group A than B and C, and in group B than C. This was in agreement with *Pogorzelska et al. (2017)* who showed that ammonia increased in LC patients infected with H pylori compared with noninfected individuals. *El-seid et al. (2015)* showed that ammonia was higher in LC patients in comparison to control group and in patients with H pylori in comparison to patients without it. *Agrawal et al. (2011)* showed that ammonia levels increased significantly in patients with minimal HE than those without. Unlike our results, *Schulz et al. (2016)* concluded that venous ammonia concentration wasn't affected by the ammonia produced by H pylori.

In our study, plasma endotoxin significantly increased in group A than B and C and in group B than C. This was in agreement with *Jain et al. (2012)* who found that serum endotoxin levels significantly increased in patient with HE and minimal HE as compared to patients without minimal HE and healthy controls. *El-Lehle et al. (2019)* found that there was a significant increase in endotoxin and arterial ammonia in LC patients than controls, with the highest levels in LC patients with HE and higher levels in comatosed patients than those in precoma. To predict HE, serum endotoxin had a sensitivity of 93%, specificity of 77% at a

cutoff point of 0.42 EU/ml, while at a cutoff point of 75.5  $\mu\text{mol/l}$  arterial ammonia had a sensitivity of 80% and a specificity of 73%. They concluded that serum endotoxin and arterial ammonia were elevated in patients with LC with higher levels in HE and the highest in hepatic coma.

In our study, HE was significantly increased in group A. This was in agreement with *Agrawal et al. (2011)* who showed that H pylori was higher in patients with minimal HE than in those without.

In contrary to our results, *Behroozian et al. (2010)* found that H pylori was higher in LC patients than healthy controls. But H pylori was not different between LC patients with HE and without HE.

Our study was limited because of the small sample size, we recommend further studies with larger number of participants.

All the participants in this research were in Egypt and we investigated persistent HCV-induced liver disease without knowing whether our findings were appropriate for other patients with other etiologies. More trials are required to show the role of eradication of H pylori in HE prevention and treatment.

## CONCLUSION

Cirrhotic patients (Child C) with positive H pylori had higher incidence of HE, higher levels of ammonia and endotoxins than patients with negative H pylori.

**Conflict of interest:** Nil.

**Funding:** Nil.

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## دراسة دور البكتريا الحلزونية في آلية إحداث الاعتلال الكبدي المخي

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قسمي الباطنة العامة والباثولوجيا الإكلينيكية، كلية طب الأزهر

**خلفية البحث:** في مرضى التليف الكبدي، يعتقد أن نشاط إنزيم اليوريز  
الخاص بالبكتريا الحلزونية هو مصدر للأمونيا المعدية.

**الهدف من البحث:** دراسة دور البكتريا الحلزونية في آلية إحداث الاعتلال  
الكبدي المخي.

**المرضى وطرق البحث:** أجريت دراسة الحالات والشواهد على 100  
مريضا، 18 عامًا أو أكثر، من كلا الجنسين. تم تقسيم المرضى إلى 3  
مجموعات؛ المجموعة أ (العدد = 40) وهم مرضى تليف الكبد (شيلد سي)  
والبكتريا الحلزونية موجبة، والمجموعة ب (العدد = 40) وهم مرضى تليف  
الكبد (شيلد سي) والبكتريا الحلزونية سلبية والمجموعة ج (العدد = 20) وهم  
الأشخاص الأصحاء كمجموعة تحكم. وقد تم إجراء مولد المضاد البكتريا  
الحلزونية في البراز والأمونيا في الدم الشرياني والسموم الداخلية في  
البلازما.

**نتائج البحث:** كان متوسط قيمة الأمونيا المصلية  $31.66 \pm 97.28$   
نانوجرام / ديسيلتر في المجموعة أ،  $14.91 \pm 65.45$  نانوجرام / ديسيلتر  
في المجموعة ب و  $11.66 \pm 48.6$  نانوجرام / ديسيلتر في المجموعة ج؛  
كانت هناك زيادة مهمة إحصائيا في المجموعة أ عن ب و ج وفي المجموعة  
ب عن ج. كان متوسط قيمة السموم الداخلية في البلازما  $0.11 \pm 0.55$   
نانوجرام / ديسيلتر في المجموعة أ،  $0.12 \pm 0.34$  نانوجرام / ديسيلتر في  
المجموعة ب و  $0.09 \pm 0.25$  نانوجرام / ديسيلتر في المجموعة ج؛ كانت  
هناك زيادة مهمة إحصائيا في المجموعة (أ) من (ب) و (ج) وفي المجموعة

(ب) من المجموعة (ج). وقد زاد زيادة مهمة إحصائياً في المجموعة (55.0%) من المجموعة (17.5%).

**الاستنتاج:** مرضى التليف الكبدي (شيلد سي) المصابين بالبكتيريا الحلزونية يعانون من ارتفاع معدل الإصابة بمرض الاعتلال الكبدي المخي، ومستويات أعلى من الأمونيا والسموم الداخلية من المرضى الذين يعانون من الملوية البوابية السلبية.