*IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)*
*e-ISSN: 2278-3008, p-ISSN:2319-7676. Volume 11, Issue 1 Ver. III (Jan. - Feb. 2016), PP 25-33*
*www.iosrjournals.org*

# A Study on the Correlation between Infection with Helicobacter Pylori and Hepatic Encephalopathy in Patients with Chronic Liver Disease

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***Abstract:***
***Background:*** *Hepatic encephalopathy is a complex neuropsychiatric syndrome occurring in patients with severe hepatic insufficiency. 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.*
***Objectives:*** *To find out whether there is any correlation between the gastric ammonia concentration and Helicobacter pylori infection of the stomach. To find out whether there is any correlation between the gastric ammonia and blood ammonia concentration and occurrence of hepatic encephalopathy in Helicobacter pylori infected subjects.*
***Materials And Methods:*** *A comparative, case-control study between June 2014 and June 2015 where 50 cases (chronic liver disease with hepatic encephalopathy) and 50 controls (chronic liver disease without hepatic encephalopathy) were selected from the indoors and outpatients of the departments of Medicine, Gastroenterology of R.G. Kar Medical College. Arterial and gastric ammonia level, RUT test for H. pylori detection and psychometric testing were performed for hepatic encephalopathy detection. (signature, construction of a standard 5-pointed star), subtraction of serial sevens, Number Connection Test (NCT) and Line Tracing Test(LTT).*
***Result:*** *The mean arterial blood ammonia level in patients with hepatic encephalopathy was 73.220± 23.234 (Range: 20-100) umol/L and that in patients without hepatic encephalopathy was 19.080± 5.337 ( Range : 11-35) umol/L. The difference in the two groups was highly significant (p=<0.0001). The mean Gastric Juice Ammonia level in patients with hepatic encephalopathy was 2.367± 0.7467 mmol/L (Range: 0.50 – 3.5) and that in patients without hepatic encephalopathy was 1.242± 0.2936mmol/L ( Range : 0.75 - 2) The difference was significant (p=< 0.0001). The prevalence of H. pylori infection was found to be significantly higher in those patients having chronic liver disease who presented with encephalopathy than who were in the control group ( i.e without encephalopathy). ( 67% VS 33%, p=0.0327 )*
***Conclusion:*** *There is a positive correlation between H. pylori infection of the stomach and the gastric juice ammonia concentration in patients with chronic liver disease. There is significant correlation between the gastric juice ammonia concentration and the occurrence of hepatic encephalopathy in-patients with chronic liver disease. There is significant correlation between H. pylori infection of the stomach and the occurrence of hepatic encephalopathy in patients with chronic liver disease.*
***Key Words:*** *CLD- Chronic liver disease, H.P.- Helicobactor pylori, R.U.T.- Rapid urease test, H.E.-Hepatic encephalopathy.*

## I. Introduction

Hepatic encephalopathy is a complex neuropsychiatric syndrome occurring in patients with severe hepatic insufficiency. The overall prevalence is not exactly known, but-fifty to eighty percent of patients with cirrhosis have some cerebral dysfunction when investigated by electroencephalography (EEG) or psychometric testing .(1)

The aetio pathogenesis of hepatic encephalopathy is an enigma. 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 alterations in the

permeability of the blood-brain barrier, abnormal neurotransmitter balance, altered cerebral metabolism, impairment of neuronal membrane sodium-potassium- ATPase activity, and abnormality in GABAergic neurotransmission.( 2)

Although plasma ammonia is not the only factor involved, it is widely accepted that it plays a pivotal role in the pathogenesis of hepatic encephalopathy in cirrhotic patients ( 3 ). In the gut, the main sources of ammonia production are the bacterial breakdown of urea and the mucosal glutamine metabolism (4 ) Although colonic bacteria are considered as the main source of ammonia, the stomach in subjects with urease producing Helicobacter pylori is seen as a potential alternative site ( 5) and *Helicobacter pylori* urease activity has been claimed as an important source of ammonia in the stomach of cirrhotics(6).Identification of Helicobacter pylori as the source of urease in the stomach in the last decade has resulted in a rebirth of interest in gastric urease and its products.

However, the data regarding the ammonia production by *H. pylori* urease in the stomach are conflicting, with gastric ammonia levels in cirrhotic patients ranging from 2.3 ± 1.9 to 61.4 ± 35 mmol/L. It would appear that the gastric ammonia levels reported ( 7 ) were too low to affect plasma ammonia levels in cirrhotics (8). On the other hand, plasma ammonia levels were found to be higher in cirrhotics with *H pylori* infection than uninfected patients in some studies (9) while others have failed to confirm this result(10). A reduction in blood ammonia levels has also been reported, with improvements in neurological status in hepatic encephalopathy after *H. pylori* eradication(7 **).**

Therefore, the suggested role of gastric infection with *H pylori* as cause of hepatic encephalopathy has still not been fully clarified. Though. there are at least three studies from the developed countries, documenting that Helicobacter pylori infection increases the risk of developing encephalopathy in the cirrhotic patients(11**)**, two other recent studies have failed to find a relationship between *H pylori*, plasma ammonia levels, and psychometric testing scores in cirrhotic patients with latent or mild hepatic-encephalopathy (12).

Chronic liver disease constitutes an important health problem throughout the world with hepatotropic viruses being the major cause of chronic liver disease in most parts of the world, (13) including our country, giving rise to a large number of patients being admitted with hepatic encephalopathy in the wards. However, data on the aetiopathogenetic factors in hepatic encephalopathy from India and other developing countries is extremely scarce.

## II. Material And Methods

**PATIENT SELECTION:** Two groups of patients were randomly selected from the indoors and outpatients of the departments of Medicine, Gastroenterology of R.G.Kar Medical College**.**

- **CASES :** Patients with chronic liver disease with hepatic encephalopathy(n=50)
- **CONTROLS :** Patients with chronic liver disease without hepatic encephalopathy(n=50)

**INCLUSION CRITERIA**

Chronic liver disease.

**EXCLUSION CRITERIA**

Patients with:

- renal failure (creatinine > 3.0 mg/dl)
- history of antibiotic intake during the preceding four weeks
- active peptic ulcer disease
- history of anti-H. pylori therapy
- any malignancy
- marked clotting impairment :

1.Prothrombin time > 33 seconds (3 x control)
2.APTT> 50 seconds or
3.Platelet count < 45.0004/Ul

- history of G.I. bleeding during the preceding four weeks
- history of alcohol intake during the preceding three months
- grades III and IV hepatic encephalopathy
- encephalopathy due to any other cause.

A total of 100 patients diagnosed by clinical, biochemical, radiological and histopathological parameters were enrolled in the study and later evaluated for aetiology. Routine ultrasonological examination (including Doppler flow study) of the upper abdomen, HBsAg and anti HCV , HBeAg and HBV

DNA were tested .( in HBsAg positive patients). HCV RNA was tested in anti-HCV positive patients. Markers for autoimmune and Wilson's disease (anti-nuclear antibody, anti smooth muscle antibody, serum ceruloplasmin, urinary copper and slit lamp examination for KF ring) were done where clinically indicated.

**Encephalopathy Determination:**

Presence of Hepatic encephalopathy was determined by clinical assessment, which included mental status (alertness, mood, memory, and orientation) and complaints of sleep pattern disturbance, i.e., day/night reversal (insomnia, daytime somnolence).

We enrolled patients, with both grade I and II hepatic encephalopathy, according to the classification suggested by **(**14), as well as those with latent hepatic encephalopathy (determined by psychometric testing). Grade I is characterized by several alterations of mental status (hypersomnia, insomnia, or inversion of sleep pattern, subtly impaired computations, shortened attention span, euphoria or depression, muscular incoordination, impaired handwriting). Grade II is usually characterized by an accentuation of the signs and symptoms of Grade I along with the presence of asterixis (flapping tremor). The patient maybe drowsy, with inappropriate behaviour, but still possesses the ability to maintain sphincter control. The latent encephalopathy is characterized by absence of clinical signs of hepatic encephalopathy and presence of abnormalities of cerebral function, as revealed by psychometric testing. (15 ) .

Psychometric testing was performed for apraxia (signature, construction of a standard 5-pointed star), subtraction of serial sevens, Number Connection Test (NCT) and Line Tracing Test (LTT).

**Endoscopic Procedures**

All the patients had fasted for 16 hours before endoscopy. . Endoscopy was carried out using an Olympus GIF XQ30 videoendoscope.

**Gastric Juice Collection**

During the endoscopy, just after entering the stomach; 5 ml of gastric juice was aspirated through the side channel of the endoscope using a suction cannula and a 20m1 syringe which was also meticulously washed with ammonia free water prior to the procedure to avoid any contamination. The gastric juice was collected in a glass vial and immediately stored in an ice box before being transferred to the laboratory.

**Detection Of Helicobacter Pylori**

After the collection of gastric juice, 3 biopsies were performed in the antrum and 3 in the gastric body. Biopsy was carried out using an Olympus FB 25K forceps. The presence of H. pylori infection was assessed by rapid urease test and histology**.** Rapid urease test (**RUT**) was performed using two biopsy specimens (one each from the antrum and body). Two of the remaining specimens (one each from the antrum and body) were stained with GIEMSA and used to determine the presence of the bacterium at the laboratories of R.G.Kar Medical College. The remaining specimens (one each from the antrum and body) were used for culture of H. pylori.

**Gastric Juice Ammonia Detection**

For gastric juice ammonia determination, the gastric juice samples were stored frozen at -20°C, until they were analyzed.

**Arterial Blood Ammonia Estimation**

Just before endoscopy, an arterial blood sample was obtained from each patient, using verified ammonia-free heparin as an anticoagulant.

**Other Routine Investigation**

A venous blood sample drawn before endoscopy was used for assessment of haematological parameters [ haemoglobin, PCV, total & differential leukocyte count and platelet count ], hepatic function [ bilirubin ( total & conjugated), ALT (SGPT), AST (SGOT), alkaline phosphatase, total protein, albumin and globulin, prothrombin time ], electrolytes sodium and potassium ], glucose, urea and creatinine.

CHILD PURG SCORE ,Modified CHILD PURG SCORE were determined.

**Statistical Analysis**

Statistical evaluation was done by the Analysis of Variance (ANOVA): single factor for unpaired data, and Chi square tests, as appropriate, using MS EXCEL Software. Differences were considered significant at a 5% probability level. All values are given as mean ± SD, unless indicated otherwise.

## III. Results

Our study was a comparative, case-control study undertaken between June 2014 and June 2015. In our study, 50 cases (chronic liver disease with hepatic encephalopathy) and 50 controls (chronic liver disease without hepatic encephalopathy) were recruited as per selection criteria.

- The mean age of patients with encephalopathy (cases) was 48.36± 9.304years.
- The mean age of patients without encephalopathy (controls) was 48.24±11.536 years.
- But the difference was not significant (p=0.9545)

**Aetiology of Chronic Liver Disease:**

- The aetiology of the chronic liver disease in the patients with hepatic encephalopathy was as follows:

ALCOHOL 42% (21patients)
HEPATITIS B 36% ( 18 patients )and
CRYPTOGENIC 14% (7 patients )
HEPATITIS C 8% (4 patients )

- The aetiology of the chronic liver disease in the patients without hepatic encephalopathy was as follows:

ALCOHOL 46% (23 patients)
HEPATITIS B in 30%, (15 patients)
CRYPTOGENIC 12% ( 6 patients )
HEPATITIS C in (6%) 3 patients,and
AUTOIMMUNE HEPATITIS 4% ( 2 patients)
WILSON'S DISEASE in (2.%) 1 patient

**The different grades of Encephalopathy were as follows:**

Subclinical Encephalopathy: 3 patients ( 6% %)
Grade I Encephalopathy : 30 patients ( 60 %)
Grade II Encephalopathy : 17 patients ( 34 %)

RUT, histology and culture was done in all patients. In the encephalopathy (case) group, H. pylori was detected in 37/50 patients (40%)[RUT], 38/50 patients (40%)[HPE] 39/50 patients (39 %)[Culture] , while in the control group, H. pylori was detected in 26/50 patients (28 %)[RUT], 27/50 patients (28 %)[HPE] , 28/50 patients (28 %)[Culture].

**Correlation between Encephalopathy and Arterial Blood Ammonia**

The mean arterial blood ammonia level in patients with hepatic encephalopathy was 73.220± 23.234 (Range: 20-100) umol/L and that in patients without hepatic encephalopathy was 19.080± 5.337 ( Range : 11-35) umot/L. The difference in the two groups was highly significant (p=<0.0001) .

**Correlation between H. pylori and Gastric Juice Ammonia**

The mean Gastric Juice Ammonia level in patients with hepatic encephalopathy was 2.367± 0.7467 mmol/L (Range: 0.50 – 3.5) and that in patients without hepatic encephalopathy was 1.242± 0.2936mmol/L ( Range : 0.75 - 2) The difference was significant (p=< 0.0001).

The mean Gastric Juice Ammonia level in patients in the encephalopathy group with H. pylori infection was 2.725 ± 0.2774 mmol/L and in the same patients without Helicobacter pylori infection was 1.095 ± 0.4015 mmol/L. The results were statistically significant (p<0.0001 ).

The mean Gastric Juice Ammonia level in patients in the control group with H. pylori infection was 1.246 ± 0.3585 mmol/L and in the same patients without H. pylori infection was 1.237 ± 0.1893 mmol/L. The results were statistically not significant (p = 0.7693 )

These results suggest that H.pylori infection is capable of increasing the ammonia concentration in the Gastric Juice by its well documented Urease activity.

**Correlation between Gastric Juice and Arterial Blood Ammonia**

A correlation analysis between the gastric juice ammonia levels and the corresponding arterial plasma ammonia levels in the patients with H. pylori infection reveals significant positive correlation, in presence of encephalopathy.

**Correlation between H. pylori and Arterial Blood Ammonia**

In the cases, the mean arterial blood ammonia level in patients with H. pylori infection was 84.641 ± 8.743 mmol/L and that in patients without H. pylori infection was 32.727 ± 6.498 mmol/L.This difference is statistically significant ( p=< 0.0001 )

In the controls , the mean arterial blood ammonia level in patients with H. pylori infection was 19.964± 6.245 mmol/L and that in patients without H. pylori infection was 17.955 ± 3.735 mmol/L . This difference is not statistically significant. (p=0.1804 )

These results suggest that H. pylori infection is capable of increasing the arterial plasma ammonia in patients with chronic liver disease, in presence of encephalopathy.

**Correlation between H. pylori and Hepatic Encephalopathy**

The prevalence of H. pylori infection was found to be significantly higher in those patients having chronic liver disease who presented with encephalopathy than who were in the control group ( i.e without encephalopathy). ( 67% VS 33%, p=0.0327 )

## IV. Discussion

HBV was the aetiological factor in 35.4% (16 ) to 80% (17 ) of patients with chronic liver disease in India, while HCV was detected in 10.8% to 26% (18 ) of patients with chronic liver disease.

In 1996,(19) have reported that HBV is responsible for 70% of cases of chronic hepatitis and 80% of cases of cirrhosis of the liver in India. Co infection with hepatitis C virus or hepatitis delta virus is comparatively uncommon. In the same year,(20) , have reported that, out of 148 biopsy-proven cases of cirrhosis, 83 (56.1%) patients had cirrhosis related to hepatitis B. Antibodies to HCV were found in 16 (10.8%) patients. Dual infection with HBV and HCV was seen in 20 (13.5%). patients. Twenty nine (19.5%) patients, had cryptogenic cirrhosis as none of the markers for HBV or HCV infection was positive. In conclusion, HBV is the most prevalent viral infection associated with chronic liver disease patients in North India.

While both these studies were based in North India, studies from South India (21)also documented a high prevalence of Hepatitis B as a cause of chronic liver disease. In Eastern India, a study from S.S.K.M. institution has shown that a total of 62/175 (35.4%) patients had HBV related CLD. HCV was present in 17/114 (14.9%) cases and none had infection with both viruses. Autoimmunity, Wilson's disease and alcohol were the aetiological factors in 5 (2.8%), 5 (2.8%) and 3 (1.7%) patients respectively. No aetiology could be found in 18/114 (15.8%) patients. The conclusion' is that, HBV is the commonest cause of CLD in Eastern India. Alcohol and HCV are uncommon in this part of the country.

But this study is a hospital based study, not a epidemiological study and done in West Bengal where due to cultural aspect alcohol is widely consumed. So in this study alcohol is commomest cause of chronic liver disease.

**Correlation between Encephalopathy and Arterial Blood Ammonia**

The mean arterial blood ammonia level in patients with hepatic encephalopathy was 73.220± 23.234 (Range: 20-100) umol/L and that in patients without hepatic encephalopathy was 19.080± 5.337 ( Range : 11-35) umot/L. The difference in the two groups was highly significant (p=<0.0001) .

In our study, we have found that arterial ammonia is significantly increased in patients with hepatic encephalopathy (73.220±23.234 vs. 19.080± 5.337 umol/L, p<0.01) but the level does not correlate well with the severity of encephalopathy. We have included only Grade I and II patients, and this could also contribute somewhat to the lack of correlation. However, previous studies have also shown that arterial blood ammonia levels are elevated in about ninety percent of patients with hepatic encephalopathy, and some patients with severe hepatic encephalopathy have normal or borderline elevation of their arterial ammonia levels. (22). Snady and Lieber have shown that encephalopathy usually becomes clinically apparent when the mean of the arterial blood ammonia levels rise above 122 umol/L.. Thus, our findings once again show that hyperammonaemia is a consistent finding in hepatic encephalopathy in patients with chronic liver disease, but the exact correlation with the degree of cerebral dysfunction needs to be determined.

**Correlation between H. pylori and Gastric Juice Ammonia**

The mean Gastric Juice Ammonia level in patients with hepatic encephalopathy was 2.367± 0.7467 mmol/L (Range: 0.50 – 3.5) and that in patients without hepatic encephalopathy was 1.242± 0.2936mmol/L ( Range : 0.75 - 2) The difference was significant (p=< 0.0001).

The mean Gastric Juice Ammonia level in patients in the encephalopathy group with H. pylori infection was 2.725 ± 0.2774 mmol/L and in the same patients without Helicobacter pylori infection was 1.095 ± 0.4015 mmol/L. The results were statistically significant (p<0.0001 ).

The mean Gastric Juice Ammonia level in patients in the control group with H. pylori infection was 1.246 ± 0.3585 mmol/L and in the same patients without H. pylori infection was 1.237 ± 0.1893 mmol/L. The results were statistically not significant (p = 0.7693 )

These results suggest that H.pylori infection is capable of increasing the ammonia concentration in the Gastric Juice by its well documented Urease activity.

Gastric ammonia production in cirrhotics infected with H. pylori could be significant, thanks to the large bacterial load generated by colonization of the fundus, facilitated by the hypochlorhydric milieu. (23 ) Thus, Helicobacter pylori urease activity is an important source of ammonia in the stomach of cirrhotics. It has been shown that that gastric ammonia levels in cirrhotic patients with H. pylori infection are higher than in cirrhotics without infection (4.58 ± 0.55 vs. 1.93 ± 0.64 mmol/L $p<0.05$). ( 24 ) Our findings (2.725 ± 0.2774 vs. 1.095 ± 0.4015 mmol/L $p<0.001$) are in complete agreement with the earlier findings in several studies.

**Correlation between Gastric Juice and Arterial Blood Ammonia**

A correlation analysis between the gastric juice ammonia levels and the corresponding arterial plasma ammonia levels in the patients with H. pylori infection reveals significant positive correlation, in presence of encephalopathy.

The bacterial urease generates a considerable amount of ammonia in the stomach, (25 ). The highest amount of gastric juice ammonia reported in cirrhotics with H. pylori infection (4.58 ± 0.55 mmol/L) .

Ammonia produced by H.pylori has a role in the pathogenesis of hyperammonemia when this organism is widely distributed and present in large numbers in the stomach, particularly in the presence of liver cirrhosis **(**26 ). However, blood ammonia concentration in H pylori-positive patients was significantly higher than that in HP KIT-negative patients ($P < 0.01$).

**Correlation between H. pylori and Arterial Blood Ammonia**

In the cases, the mean arterial blood ammonia level in patients with H. pylori infection was 84.641 ± 8.743 mmol/L and that in patients without H. pylori infection was 32.727 ± 6.498 mmol/L.This difference is statistically significant ( $p=< 0.0001$ )

In the controls , the mean arterial blood ammonia level in patients with H. pylori infection was 19.964± 6.245 mmol/L and that in patients without H. pylori infection was 17.955 ± 3.735 mmol/L . This difference is not statistically significant. ($p=0.1804$ )

These results suggest that H. pylori infection is capable of increasing the arterial plasma ammonia in patients with chronic liver disease, in presence of encephalopathy.

Early studies of patients with liver disease reported increased gastric urease activity associated with elevated gastric and blood ammonia levels and the frequent colonization of the upper small bowel with urea-splitting bacteria.( 27) More recently, H. pylori, with its high urease activity, have been found to contribute to blood ammonia levels in experimental models of cirrhosis, (28) and higher blood ammonia levels were present in infected, azotemic, noncirrhotic subjects. **(**29 )

Therefore, a logical conclusion should be the elevation of plasma ammonia levels in patients with chronic liver disease harbouring H. pylori infection.

**Correlation between H. pylori and Hepatic Encephalopathy**

The prevalence of H. pylori infection was found to be significantly higher in those patients having chronic liver disease who presented with encephalopathy than who were in the control group ( i.e without encephalopathy). ( 67% VS 33%, $p=0.0327$ )

It have previously reported that ammonia level in portal vein blood of cirrhotic patients with H pylori infection is significantly higher than that in patients without infection **(**30 ) In that present study, HE was more frequently observed in patients with H pylori infection than in those without (58.5% Vs 30.6%, $P < 0.01$), which was consistent with that reported elsewhere (31).The hypothesis that H pylori infection plays a pathogenic role in HE was initially devised by Gubbins et al 1998. In their study, seroprevalence for H pylori was detected in 78.6% of 117 alcoholic liver disease patients with HE, and in 62% of 71 patients without ($P = 0.013$). H pylori was detected only by serology, which has been reported to be inaccurate in cirrhotic patients. Therefore, the results of that study should be interpreted with caution. In a study of 55 cirrhotic patients, Dasani et al.1998 detected H pylori infection more frequently in those with HE compared with those without (67% vs 33%, $P = 0.004$).

## V. Conclusion

**Our study has shown that:**

Arterial blood ammonia concentration is elevated in patients with hepatic encephalopathy ($p<0.0001$), but a definite cut off value is difficult to decide upon.

The severity of hepatic encephalopathy does not correlate with the degree of elevation of arterial blood ammonia levels in patients with chronic liver disease.

There is significant difference in the prevalence of H. pylori infection in patients of chronic liver disease, with hepatic encephalopathy. ( $p=0.0327$)

There is a positive correlation between H. pylori infection of the stomach and the gastric juice ammonia concentration in patients with chronic liver disease.

There is significant correlation between the gastric juice ammonia concentration and the arterial blood ammonia concentration in patients with chronic liver disease.

There is significant correlation between the gastric juice ammonia concentration and the occurrence of hepatic encephalopathy in-patients with chronic liver disease.

There is significant correlation between H. pylori infection of the stomach and the occurrence of hepatic encephalopathy in patients with chronic liver disease.

**Limitation**

This is a cross-sectional, case-control study, which seeks to find an association between H. pylori infection and hepatic encephalopathy. It suffers from the inherent demerits of such a study.

Strict adherence to the selection criteria, led to the exclusion of a large number of patients of hepatic encephalopathy, and hence the sample size could not be reasonably large.

Grade III and IV encephalopathy patients could not be included in this study, as upper GI endoscopy should not be performed on such patients. Hence, a conclusion" cannot be drawn for this category of patients.

An interventional study in the form of H. pylori eradication therapy would have helped to establish the correlation and to assess the effects of such therapy on the arterial blood ammonia levels. We hope that a future study would incorporate it.

Many patients with subclinical encephalopathy were probably missed as VEP (Visual evocked potential ) study could not be performed in our study.

In conclusion, this study finds a correlation between H. pylori infection, plasma ammonia levels and intellectual function in cirrhotic patients with subclinical or mild overt (Grade I and II) hepatic encephalopathy. Further studies are warranted to establish whether H. pylori eradication could be a new approach to the management of hepatic encephalopathy.

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## Figures And Tables

**Figure1: Aetiology Of Chronic Liver Disease In The Study Population**

**Aetiology of chronic liver disease in cases**

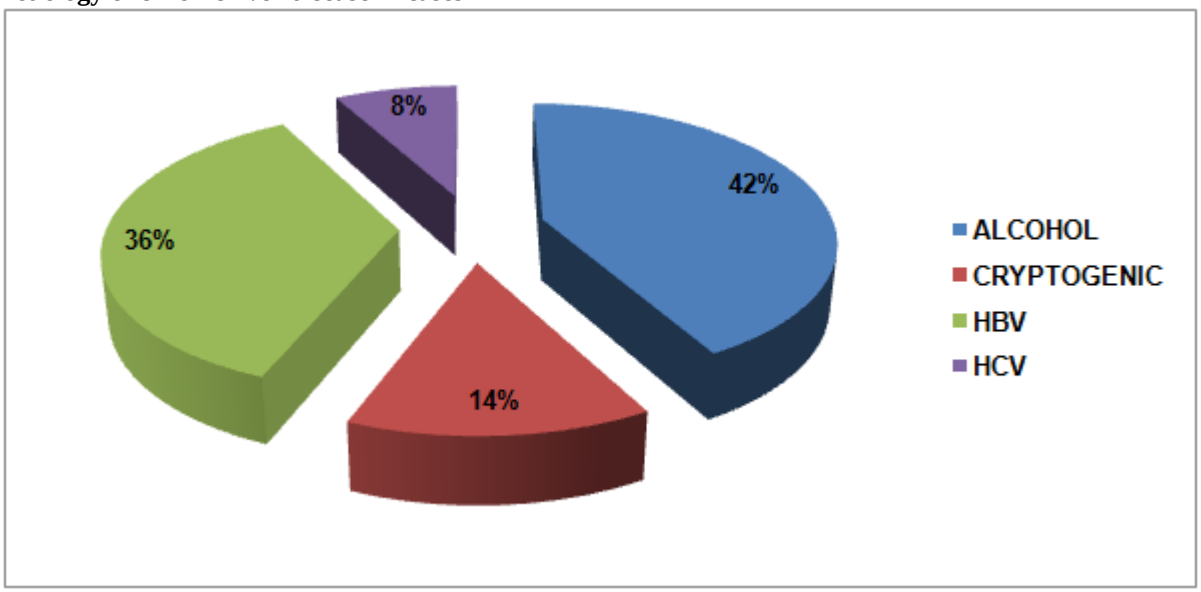


**Figure2: Aetiology Of Chronic Liver Disease In Controls**

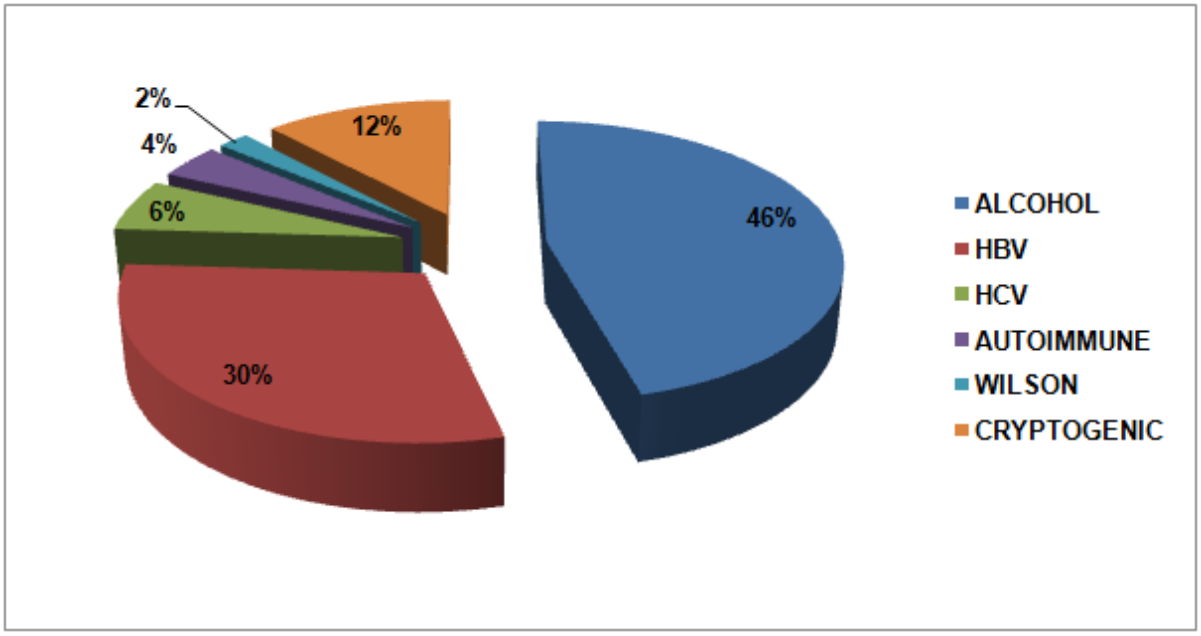

**Figure3:**

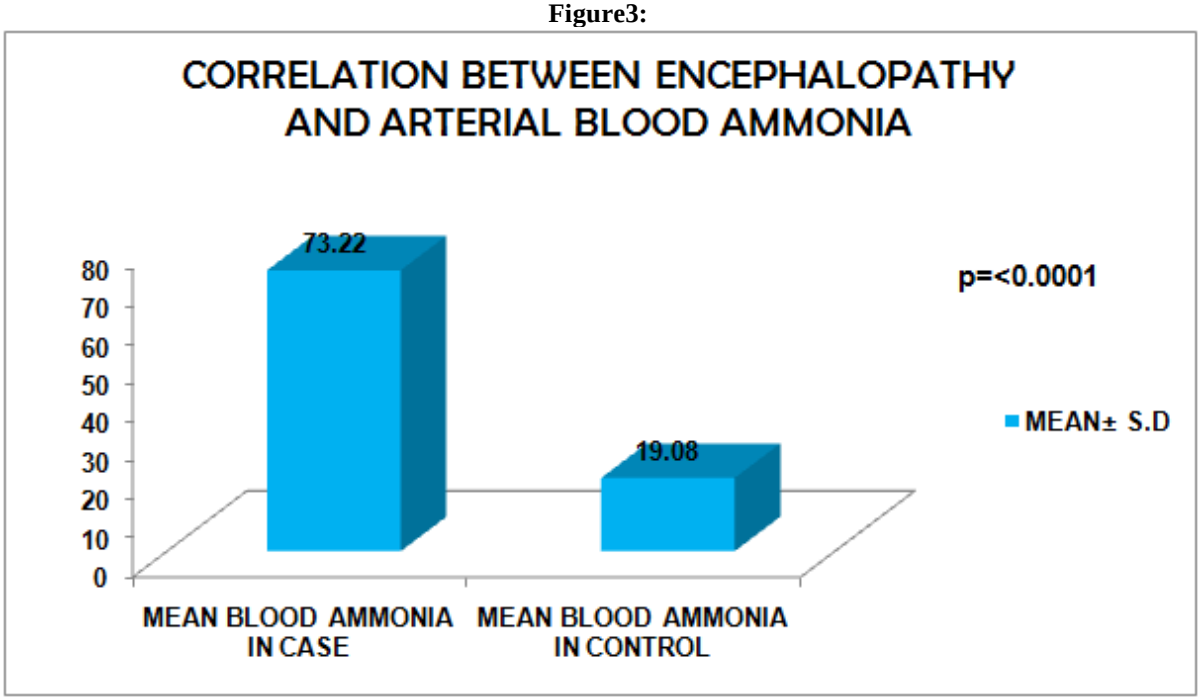


**Figure4: Correlation Between H. Pylori And Hepatic Encephalopathy**