Relation between IL-6 Serum level and stage of Hepatic Encephalopathy in Patients with Liver Cirrhosis

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Abstract: Introduction: It was found that there is a statistically significant difference between TNF-a, IL-6 levels in patients suffering cirrhosis with and without HE. In addition, there is a statistically significant difference in the receptor level of these cytokines between healthy subjects and those who suffer HE. **Aim of the Work**: Relation between IL-6 Serum level and stage of Hepatic Encephalopathy in Patients with Liver Cirrhosis. **Patients AND Methodology** Case – control study comparing IL-6 serum level between group 1(patients with only liver cirrhosis) represents controls and group 2 (patients with liver cirrhosis suffering from different grades hepatic encephalopathy) represents cases. **Results:** Median IL-6 serum Level was found to have highly significant difference between cases and controls with a median of 123.5(59.375-226.6) (pg/ml) for cases and of 14.7(5.275-44.7) (pg/ml) for controls. It was found also that there is no statistically significant relationship between IL-6 level and neither MELD Score nor Grade of hepatic encephalopathy with (R:0.07, P:0.714) for grade of HE, and (R:0.264, P:0.158) for MELD Score. **Conclusion:** From this study we concluded that IL-6 is increased significantly in patients with liver cirrhosis suffering from hepatic encephalopathy more than those with only cirrhosis without prescence of significant relation to the grade of hepatic encephalopathy.

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Key Words: IL-6, liver cirrhosis, hepatic encephalopathy, cytokines, grades.

1. Introduction:

Cirrhosis represents the final common histological pathway for a wide variety of chronic liver diseases. The term cirrhosis was first introduced by Laennec in 1826. It is derived from the Greek term scirrhus and is used to describe the orange or tawny surface of the liver seen in autopsy**. (Riggio et al, 2005).** Hepatic encephalopathy (HE) is a well-recognized and commonly diagnosed syndrome associated with advanced chronic liver disease and its clinical manifestations range from sleep disturbance toconfusion or coma **(Ferenci et al, 2002).** In rarecases, hepatic encephalopathy presents with overt seizure activity. **(Ficker et al, 1997).** Recent studies indicate that mediators of inflammation (tumor necrosis factor-alpha (TNF-α), interleukin-I beta (IL-I β), interleukin-6 (IL-6) may exacerbate the effects of ammonia on the brain leading to more exacerbation of encephalopathy. **(Shawcross et al, 2004).** In addition, there was statistically significant difference between patients without hepatic encephalopathy and healthy patients in term of serum TNFα, IL-6, IL-8, IL-12 receptor level**. (Odeh et al, 2005).** IL-6 is a pleiotropic cytokine with a wide range of biological activities in immune regulation, hematopoiesis, inflammation and oncogenesis. Its activities are shared by IL-6-related cytokines such as leukemia inhibitory factor (LIF), cilliary neurotrophic factor (CNTF) and oncostatin. **(Kishimoto, 2005).** Patients with liver cirrhosis are functionally immunosuppressed and are consequently prone to developing infections. Systemic inflammatory response syndrome (SIRS) results from the release of proinflammatory cytokines into the circulation due to liver damage and local or systemic infection**, (Shawcross et al, 2010).**

There is evidence that the nature and extent of both SIRS and neuroinflammation are dependent on the etiology and severity of liver injury. A number of studies using animal models of minimal HE in the last 3 years have addressed the issue of the role of inflammation in the pathogenesis of CNS symptoms, and in some of these studies, central neuroinflammation was assessed. End-to-side portacaval anastomosis in the rat was found to result in increased brain concentrations of the proinflammatory cytokine IL-6 as well as increased activities of cyclooxygenase and inducible nitric oxide synthase. However, microglial activation was not assessed in these animals, and improvements in learning skills following ibuprofen administration occurred without a significant reduction in cytokine levels **(Cauli et al, 2007).** In a more recent study locomotor activity deficits in rats with portal vein ligation were accompanied by increased expression of IL-6 messenger RNA without any evidence of microglial activation. The identity of the cell responsible for IL-6 expression was not established in

that study, **(Bru¨ck et al, 2011, D'Mello et al, 2009).** Recent studies indicate that mediators of inflammation (tumor necrosis factor-alpha (TNF-α), interleukin-I beta (ILIβ), interleukin-6 (IL-6)) may exacerbate the effects of ammonia on the brain **(Shawcross et al, 2004).**

The aim of the work: is to estimate the relationship between IL-6 serum level and different stages of hepatic encephalopathy in Egyptian cirrhotic patients.

Patients and methods:

A Case – control study on 60 subjects; of cirrhotic patients admitted in Theodor Bilharz Institute hospital during the time period from January 2012 to July 2012, with age ranging from 20 – 65 years they were divided into Group I (Case group) which Included 30 patients diagnosed as Patients with liver cirrhosis due to any cause, depending on history, clinical examination, liver function tests, viral markers and ultrasound imaging suffering from Hepatic encephalopathy of different grades and Group II (Control group) which Included 30 Patients with only cirrhotic liver without any other medical conditions.

Results:

Table (1): comparison between vital data in patients and control:

	Patients Mean ± SD	Control Mean ± SD	P value	Significance
Age (years):	**57.13 ± 6.044**	**56.4±5.581**	**0.627**	**N S**
Systolic pressure (mm Hg)	**111 ± 12.959**	**112 ± 12.429**	**0.761**	**NS**
Diastolic pressure (mm Hg)	**67.67 ± 7.279**	**67.33 ± 7.849**	**0.865**	**NS**
Heart rate (beat/minute)	**90.4 ± 4.048**	**90.17 ± 4.332**	**0.83**	**NS**
Temperature (degree Celsius)	**37.063 ± 0.2773**	**37.05 ± 0.2636**	**0.849**	**NS**
Urine output (cc/24 hours)	**2295 ± 589.762**	**2145±586.684**	**0.327**	**NS**

Table (2): Comparison between mean renal, and liver fuctions:

	Patients	Control		
	Mean ± SD	**Mean ± SD**	**P Value**	**Significance**
Sodium (mEq/L)	**120.77 ± 4.629**	**135.83 ± 3.582**	**< 0.001**	**H S**
Potassium (mEq/L)	**3.54 ± 0.5042**	**3.913 ± 0.3748**	**0.002**	**H S**
Creatinine (mg/dL)	**1.3343 ± 0.45771**	**1.12 ± 0.37083**	**0.051**	**N S**
BUN (mg/dL)	**43.9 ± 12.906**	**26.93 ± 10.68**	**0**	**H S**
	Median(Percentiles)	**Median(Percentiles)**	**P Value**	**Significance**
ALT (U/L)	**35(25-52.5)**	**25.5(19-39.75)**	**0.029**	**S**
AST (U/L)	**68(58.25-111.5)**	**46.5(38.5-58.5)**	**0**	**H S**
Total bilirubin (mg/dL)	**2.4(1.8-6)**	**1.85(1.45-4.4)**	**0.064**	**NS**
Direct bilirubin (mg/dL)	**1.8483(5-0.775)**	**0.7(0.45-1.425)**	**0.004**	**HS**
	Mean ± SD	**Mean ± SD**		
Albumin	**2.567 ± 0.5536**	**2.573 ± 0.4378**	**0.062**	**N S**

Table (3): Comparison between Median IL-6 Level in patients and control:

	Patients	Control		
	Median (percentiles)	**Median (percentiles)**	**P Value**	**Significance**
IL-6 Level (pg/ml):	**123.5(59.375-226.6)**	**14.7(5.275-44.7)**	**0**	**HS**

Table (4):Relatonship IL-6 level and Grade of Hepatic encephalopathy:

	Grade Of HE.		
	R value	**P value**	**Sig.**
IL-6 LEVEL	**0.07**	**0.714**	**NS**

4. Discussion:

In our study there was a significant difference between IL- 6 level in serum with median (14.7(5.275-44.7)) pg/dl in controls (patient suffer only from liver cirrhosis) and (123.5(59.375-226.6)) pg/dl in cases (patient suffer from liver cirrhosis and different grades of HE), and that was nearly similar with **Vedat Goral et al, 2010** which showed median of 70 pg/dl for cases and 30 pg/dl for the controls, and it was also similar to **Lokesh et al, 2012** which concluded that Median arterial ammonia, tumour necrosis factor-alpha, Interleukin-6, Interleukin-18

and serum endotoxin levels were significantly higher in patient with hepatic encephalopathy and minimal hepatic encephalopathy as compared to patients without minimal hepatic encephalopathy and healthy controls. Arterial ammonia (r=0.72, p=0.03), tumour necrosis factor alpha (r=0.87, p=0.02), Interleukin-6 (r=0.50, p=0.05), and it was similar also to **Odeh et al, 2005,** who stated that there was a statistically significant difference between TNF-a, IL-6 levels in patients suffering cirrhosis with and without HE. In addition, there is a statistically significant difference in the receptor level of these cytokines between healthy subjects and those who suffer HE, and this can be attributed to Systemic inflammatory response syndrome (SIRS) results from the release of proinflammatory cytokines into the circulation due to liver damage, and to that recent studies indicate that mediators of inflammation (tumor necrosis factor-alpha (TNF-α), interleukin-I beta (ILIβ), interleukin-6 (IL-6)) may exacerbate the effects of ammonia on the brain **(Shawcross et al, 2004).**

Also in our study there was non significant relation ship between serum IL-6 level and the grade of hepatic encephalopathy with (r:0.07, p:0.745) and that was similar to the results of **Vedat Goral et al, 2010** with (p value > 0.05) regarding correlation between IL-6 serum level and different grades of hepatic encephalopathy.

Conclusion:

From our study we have concluded that: IL-6 serum level is increased significantly in patients with liver cirrhosis with hepatic encephalopathy more than that of other patients who suffer only liver cirrhosis an this can be applicable in absence of other end organ failure, hepatocellular carcinoma and other active acute inflammatory process. And that IL-6 serum level is not related to the degree of hepatic encephalopathy in patients suffering from liver cirrhosis with grading of hepatic encephalopathy according to West Haven scoring system.

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