Role of Interleukin 6 as a Predictor of Hepatic encephalopathy in Critically Ill Cirrhotic Patients

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Abstract: Introduction: Recent studies indicate that mediators of inflammation (TNF-α), (IL- I β), (IL-6) may exacerbate the effects of ammonia on the brain leading to more exacerbation of encephalopathy. **Aim of the Work**: This study was performed to estimate the role of IL-6 in diagnosis of hepatic encephalopathy. **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 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. Also there was highly significant difference between different stages of liver cirrhosis according to Child Pugh classification regarding IL-6 serum level. with median of 6.35(4.025-9.75) (pg/ml) for child A, 35.6(28.8-58.8) (pg/ml) for child B, and161.2(45.3-180.3) (pg/ml) for child C. C**onclusion:** 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.

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Key Words: IL-6, liver cirrhosis, hepatic encephalopathy, ammonia, microglia.

1. Introduction

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 to confusion or coma ***(Ferenci et al, 2002)***. In some cases, hepatic encephalopathy presents with overt seizure activity. ***(Ficker DM et al, 1997)***.When neurological deficits are subtle but the neurological clinical examination is normal, a condition referred to as minimal HE***.(Ortiz et al,2005),*** patients are exposed to a risk of developing clinical episodes of HE over time***. (Romero-Gomez et al., 2001)***.Tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) are pleiotropic cytokines with numerous immunologic and metabolic actions***. (Tracey and Cerami,1994).*** IL-6 is an interleukin that act as both pro-inflammatory and anti-inflammatory cytokine. it is secreted from macrophages and T-cells to stimulate immune response***. (van der Poll.,1997)***. IL-6 is also a myokine which secreted from the muscle cells and elevated in response to muscle contraction.***(Febbraio and Pedersen,2005).*** Also, IL-6 has a direct mitogenic effect on hepatic stellate cells.the presence of more prominent raise in IL-6 serum level in HCC may be linked to mitogenic effect of IL-6***. (Toda.,2000).***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., 2004).***

Aim of the work

The aim of the work is to estimate the role of IL-6 in diagnosis of hepatic encephalopathy in patients with cirrhotic liver.

2. Patients and Methods

Subject study: Case – control study.

Subjects: 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.

The subjects were divided into two main groups:

Group I (Case group):

Includes 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.

Group II (Control group)

Includes 30 Patients with only cirrhotic liver without any other medical conditions.

The two groups were matched for age, sex and weight.

Exclusion criteria:

1- Other end organ failure.
2- Associated Hepatocellular carcinoma.
3- Associated acute inflammatory process.

All subjects selected were subjected to the following:

1)Full clinical history taking including manifestations of liver cell failure.
2) Detailed clinical examination.
3)Laboratory work up including; CBC, coagulation profile, renal function tests & liver Function tests.
4) IL-6 Level in blood.
5) Pelviabdominal ultrasound Imaging.

3.Results

This study was a case-control study carried out on 60 Egyptian patients having liver cirrhosis admitted in Theodor Bilharz hospital,,30 of them were having only liver cirrhosis set as controls, and 30 of them were having also HE. Set as cases, with age and sex matched between both groups.

The patients were 34 males (56.66%) and 26 females (43.33%), their age ranged from 45– 65 years with mean age 57.13 years for encephalopathic patients,and 40-65 years for control patients suffering from liver cirrhosis only with mean age 56.4 years. These patients were diagnosed as cirrhotic patients by abdominal ultrasound and liver function tests with mean duration of cirrhosis 5.65 ± 5.36 years. Only 4 patients (6.66%) showed no signs of decompensation, while the other 56 patients 93.33% showed variable signs of decompensation (ascites, encephalopathy, hyperbilirubinemia), of variable durations, ranging from 6 months – 8 years, with mean duration of 2.13 ± 2.22 years. All the patients have been subjected to detailed history taking & full clinical examination, and it was found that 14 patients (68.995%) had manifestations of (soft hair, palmar erythema, Terry's white nail, paper money skin). It is well known that the most common causes for hospital admission in hepatic patients are encephalopathy, hematemisis, melena, L.L oedema and ascites, it was found that 38 patients (63.33%) were suffering from ascites, 30 patients (50%) were having encephalopathy of different degrees, 13 patients (21.66%) were admitted with combined heamatemesis and melena, 9 patients (15%) were having L.L oedema,7 patients (11.66%) were admitted with isolated melena.

Table (1): Comparison between liver enzymes and function in patients and control:

	Patients	Control		
	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 (g/dL)	2.567 ± 0.5536	2.573 ± 0.4378	0.062	N S

Table (2): Comparison between Median IL-6 Level in patients and control:

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

Table (3): Comparison between Median MELD Score in patients and control:

	Patients	Control		
	Median (percentile)	Median (percentile)	*P* Value	Significance
MELD Score:	17.5 (15-22.25)	15 (11 - 19)	0.022	S

Table (4):Comparison between IL-6 level and Child Pugh classification in cases and controls:

		Patients		Control
	NO. Of Cases	IL-6 Level: (pg/dl) Median (percentiles)	NO. Of Control	IL-6 Level: (pg/dl) Median (percentiles)
Child (A)			16	6.35(4.025-9.75)
Child (B)	12	72.35(57.125-115.65)	11	35.6(28.8-58.8)
Child (C)	18	182.15(118.125-423.725)	3	161.2(45.3-180.3)
P value: 0			P value: 0	
Significance: HS			Significance: HS	

Table (5):Relatonship between MELD Score,IL-6 level and Grade of Hepatic encephalopathy:

	Grade Of HE.			MELD Score.		
	R value	***P* value**	**Sig.**	**R value**	***P* value**	**Sig.**
IL-6 LEVEL	**0.07**	**0.714**	**NS**	**0.264**	**0.158**	**NS**

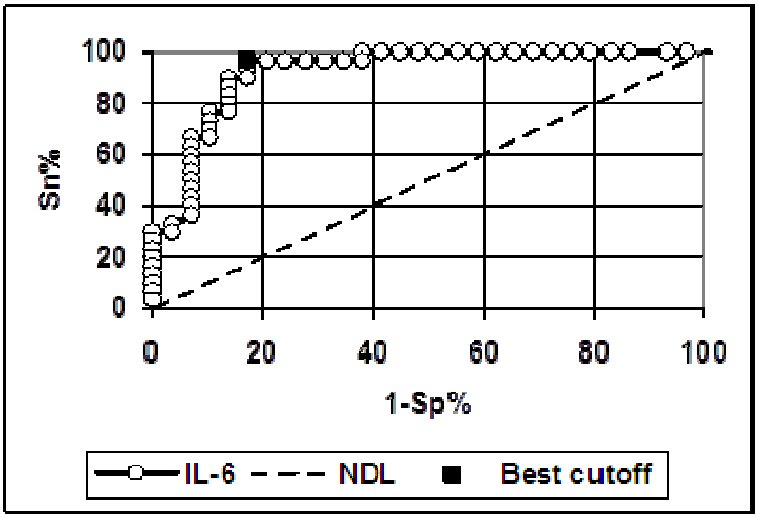

Fig. (1): ROC curve analysis showing the diagnostic performance of IL-6 for discriminating patients with hep. Enceph. from those without.

4. Discussion

Cirrhosis is defined histologically as a diffuse hepatic process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules. The progression of liver injury to cirrhosis may occur over weeks to years ***(Schuppan and Afdhal, 2008).*** Hepatic encephalopathy (HE) is a potentially serious disturbance in central nervous system function that can result from hepatic insufficiency**.** ***(Frederick, 2011).*** The exact mechanisms underlying this neurologic dysfunction have not been completely elucidated, but cerebral edema appears to be involved in this process. Glutamine (derived from glutamate and ammonia) is produced within astrocytes in the brain. This glutamine attracts water and causes swelling of astrocytes..***(Frederick,2011).*** 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).*** There is evidence suggests that toxins generated by the failing liver may play a role in the pathogenesis of neuroinflammation. A wide range of molecules including IL-6 with the potential to threaten the functional integrity of the brain have the capacity to trigger the transformation of microglia from the resting state to the activated state**.** ***(van Rossum and Hanisch,2004)***. we have demonstrated that ALT was not markedly elevated in the cases, as all the patients were chronic patients with no recent active disease, where the mean ALT for the cases was (40.03 ± 16.412) U/L, while the mean ALT for the control was (33.07 ± 20.735) U/L. The significant difference was in the AST, where the mean AST for the cases was (85.17 ± 37.421) U/L, while the mean AST for the control was (53.7 ± 23.032) U/L. The results were nearly similar to ***Ansar et al., 2009*** which showed mean AST (82.58 ± 41.77) U/L, but ALT was much higher in that study with mean (103.10 ± 63.76) U/L and it could be attributed to presence of many patients with recent diagnosis of cirrhosis which showed some activity of hepatitis.

There were significant findings in our study in the laboratory results reflecting liver function, where the mean total bilirubin for the cases was (2.867 ± 2.1546) mg/dL, it was biphasic hyperbilirubenimia where the mean direct bilirubin for the cases was (1.0367 ± 1.01861) mg/dL, this total bilirubin level was lesser than that of ***Siegfried and Berendsohn 2011*** which had mean bilirubin level of 3.9 mg/dL. The mean serum albumin in our study was (2.567 ± 0.5536) g/dL which is lesser than that of ***Scolapio et al., 2000*** which had mean serum albumin of 2.97 g/dL, and this can be attributed to the poor nutritional status of our patients, and poor albumin supplementation for them during hospital

stay. 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. There is a big dilemma regarding relationship between serum IL-6 level and Child Pugh classification. In our study there was significant relationship between serum IL-6 level and different classes of Child Pugh Classification in both cases and controls with median (72.35(57.125-115.65)) pg/dl for Child B,and (182.15(118.125-423.725 pg/dl) for Child C, regarding cases, and median (6.35(4.025-9.75 pg/dl) for Child A, (35.6(28.8-58.8 pg/dl) for Child B,and (161.2 (45.3-180.3)) pg/dl for Child C regarding controls, with(p:0) for both cases and controls and that was similar to ***Genesca, 2000,*** who stated that interleukin-6 levels has significant correlations with Child score, plasma renin activity, serum and urinary sodium, and mean arterial pressure (r > or = 0.4, *p* < 0.005), but was against ***Vedat Goral et al.,2010,***who stated that there was no statistically significant relationship between serum IL-6 level and different classes of Child Pugh classification included in this the dual correlations regarding A and B, B and C, A and C. This dilemma may be mostly due to socioeconomic and environmental factors.

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.

Also we concluded that IL-6 is significantly related to degree of liver cirrhosis according to Child Pugh classification.

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