The Role of IL-4 and IL-10 among Chronic Hepatitis Patients

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Abstract

Background: Hepatitis viruses are common cause of viral hepatitis, it has a varied distribution among people, it has more than five common types: Hepatitis A, B, C, D, E. Hepatitis B,C,&D occurred by parenteral route. Hepatitis E occurres specially in pregnant women by feco-oral route. Interleukin-4 (IL-4) protect human hepatocellular cell line from apoptosis and suppresses the expression and replication of hepatitis B virus. Exposure to HCV antigens increased L-10 production by polymorphonuclear cells and T cells.

Aim of study: To monitor the significance of IL-4 and IL-10 among patients with chronic HBV and HCV, to find the frequency of confirmed hepatitis virus in Babylon City and to compare between their percentages and possible cause of transmission and method to prevent it

Materials and Methods: A total number of 18 patients for each group of hepatitis B and C were taken to estimate of IL-4 and IL-10 which compared with 14 apparently healthy control group in Central Public Health Lab/ Babylon during the period from January-June, 2008.

Results: The results showed highly significant decrease in IL-4 in both groups in comparison to control group while IL-10 showed highly significant increase in both group in comparison to control group.

Conclusions: Immune factors are essential in the consequence of chronic HBV and HCV infection. Serum IL4 might be used as a laboratory parameter to indirectly assess liver damage instead of invasive histopathological examination. IL-10 might influence HCV and HBV infections susceptibility due to its anti-inflammatory action. IgG4 might further aggravate the disease course of HBV and HCV infection caused by IL-10.

Keywords: hepatitis B virus and hepatitis C virus, Interleukin-4, Interleukin-10

Introduction

Viral hepatitis caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) constitutes a major economic and public health problem in the world due to high rate of morbidity, mortality and development of chronic carrier state(1-3). Hepatitis B virus (HBV)is the smallest human DNA virus and had a very compact genome, belongs to the family Hepadnaviridae, which involves a group of highly species – specific DNA virus (4). HCV is an RNA virus with lipid coat like flaviviridae family. Chronic HBV was usually defined as detectable hepatitis B surface antigen (HBs Ag) for a period of six months or more (5). Researches showed that the world prevalence of HBs Ag carriers was from 0.1% till 20% with high ratio in tropical countries (6&7). The chronic form of hepatitis B was characterized by several phases, including immunotolerance, long-lasting

hepatitis with positive or negative HBe Ag, as well as the chronic disease carrier(8-10). HCV had been shown to be an etiologic agent responsible for chronic liver disease, with eventual development of cirrhosis and hepatocellular carcinoma. While the immunologic mechanisms in chronic HCV infection have not been clearly defined, it is believed that cytokines were involved (11). This complex clinical framework was the result of the interaction of factors inherent to the host and the virus, as well as environmental conditions, but is related primarily to the age and immunological status of the infected person (12-15). The understanding of the complex virus–host interaction which resulted in a variety of clinical manifestations, necessarily required a good working knowledge of the immunopathogenesis of the disease and the importance of the immunological profile of the host and its cytokine secretion pattern(16&17). In addition, the function of T helper type 1 (Th1) and Th2 cytokines were wide-ranging and include regulatory signals for activation, growth and differentiation of cytotoxic lymphocytes, macrophages, natural killer cells and granulocytes. Previous studies have inspected the role of cytokines, including tumor necrosis factor, IL1, IL2, IFN- α and IFN-γ, in hepatitis B and HIV. However, there had been little studies that specifically analyzed the levels of immunoregulatory cytokines in these chronic infections (18). However, in the context of an inflammatory response against a virus, cytokines might also clue to liver damage (19) and led to changes in liver enzymes e.g. ALT which is mostly concentrated in liver and released into the bloodstream as the result of liver injury. It, therefore, serves as a fairly specific indicator of liver status (20). For this purpose, this study aimed to find the frequency of confirmed hepatitis virus in Babylon, monitor the significance of IL-4 and IL-10 among chronic hepatitis patients and to compare between their percentages and possible cause of transmission and method to prevent it.

Patients and Methods

Patients and control :

A total of (18) patients with HCV and (18) patients also with HBV infection who consulted Central public Health Laboratory during the period from January - June ,2008 were enrolled in this study. In addition (14) individuals who were apparently healthy and consulted Central Public Laboratory for other purposes were included as a control group.

Blood aspiration:

A volume of 7 ml venous blood sample was taken from all patients and control individuals for detection of HBs antigen and anti-HCV antibody to confirm the ELISA results obtained from Central Public Health Laboratory. Blood sample was divided into two volume, one used for Polymerase chain reaction technique and the second was used for ELISA technique. The ELISA samples were centrifuged and sera were separated until time of testing.

Method:

The ELISA technique:

It was used for testing the samples by a sandwich principle. The initial diagnosis was a positive anti HCV antibody and HBS antigen from data supplied from Central Public Health Laboratory (Biotest United Biomedical Inc. USA). Serum anti-HCV antibody and HBS antigen were repeated again by third-generation ELISA (CTK-Biotech, USA) to confirm the serological diagnosis of Central Health Laboratory. IL-4 (Biosource, USA) and IL-10 (Marseille / France) were also assessed by ELISA technique.

Polymerase chain reaction technique:

Detection of HCV RNA

HCV RNA preparation and cDNA synthesis had done according to (21). Recycling of the extracted RNA was done as a template and amplified via RT-PCR with primers that were precise with 5UTR of HCV (22&23). PCR product were re-amplified by the same cyclic program, and for each pair of primer, negative controls that lacking template were included. If a control was positive, all PCR products were considered contaminated products and then discarded. Electrophoresis with 2.0% agarose gel of amplified cDNA was done to detect the amplicon of PCR product.

Detection of HCV genotypes

HCV genotypes were done by core region amplification with primers that were genotype specific (genotypes 1, 2, 3 and 4)(24&25). Fragment of HCV core gene (272 bp) was amplified with universal primers from HCV cDNA. A portion of the product was then amplified through universal sense primers by PCR and a mixture of five antisense primers gathered from HCV core gene sequences specific for HCV genotypes (1, 2, 3 and 4)(26&27).The four genotypes were differentiated from each other by PCR products size: (123, 211, 240 and 188 bp) for genotype 1, 2,3 and 4 respectively.

Radial immunodiffusion (RID): (RID)(Fitzgerald industries Int, USA).

RID (Mancini) method was the diagnostic method that used to determine IgG4 subclasses in agar plates (ready for use), holding the specific anti-IgG4 subclass antibodies. Test samples, control and standard sera were prepared to be added to the plates. After incubation for 48-72 hours at room temperature, the immunoprecipitation rings diameters were measured. The IgG4 subclass levels in the test samples was quantified by calibration curve procedure where concentrations of the standards and ring diameters were plotted and the values of tested samples were determined by interpolation.

Statistical methods

All data were presented as means and the deviations were presented as standard deviation, and to test the significance in means of different quantitative data, independent sample t- test of significance was applied. Correlation analysis was done in SPSS version 15.0. P value below 0.05 was accepted as statistically significant value.

Results

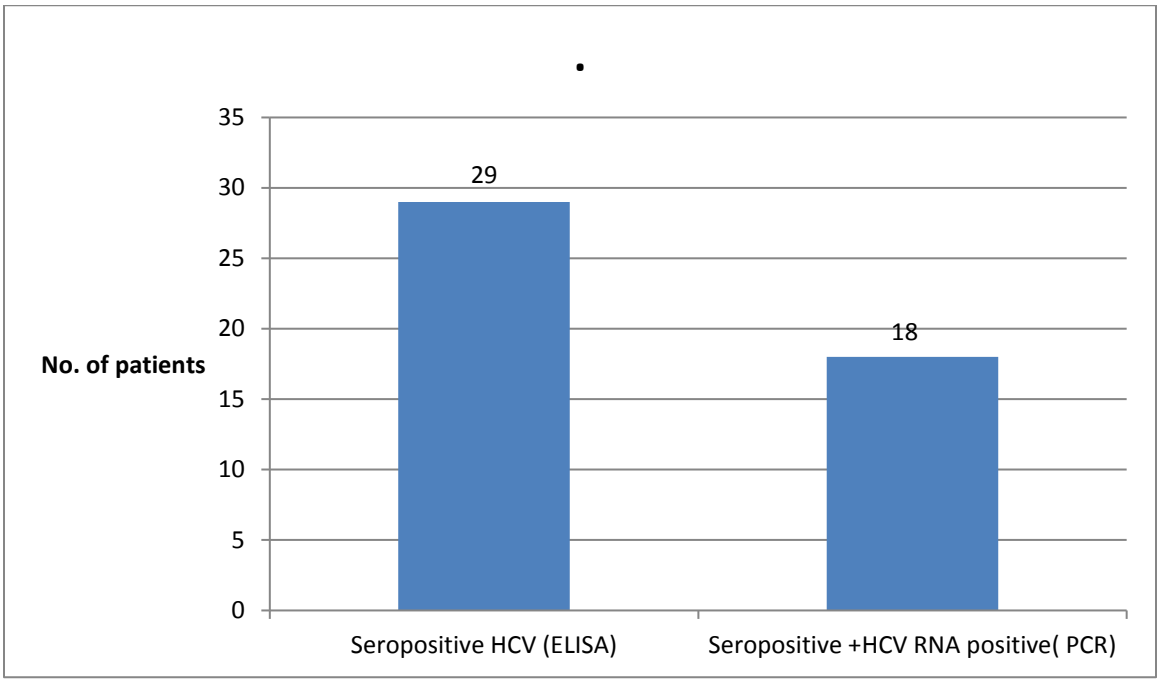

Figure (1): Frequency of confirmed HCV infection(by PCR) among seropositive HCV patients. This showed that out of 29 patients with positive anti HCV infection, only 18 case (62.06%) had positive HCV RNA confirmed by molecular technique (PCR).

Table (1): Frequency of asymptomatic and symptomatic HCV and HBV infection This showed that 7 out 18(38.89%) HCV infections were asymptomatic and the remaining 11 out 18 (61.11%) were symptomatic HCV infections while 6 out of 18 (33.33%) were asymptomatic and the remaining 12 out of 18 (66.67%) were symptomatic HBV infections.

Chronic infection		No	%
HCV Total(18)	Asymptomatic	7	38.89
	Symptomatic	11	61.11
HBV Total(18)	Asymptomatic	6	33.33
	Symptomatic	12	66.67

Table (2): Mean levels of IL-4 among patients with HBV and HCV infections. This showed that IL4 was significant decrease in asymptomatic chronic HBV and HCV in comparison to control (P value < 0.05) while it was significantly decreased in patients with symptomatic HCV and chronic HBV infection in comparison to control group (P value < 0.001).

Infection		IL-4		Control		P value
		Means	SD	Means	SD	
Patients with HCV chronic hepatitis	Asymptomatic	5.46	1.02	12.34	1.38	< 0.05
	Symptomatic	1.56	0.76	12.34	1.38	< 0.001
Patients with HBS chronic hepatitis	Asymptomatic infection	4.59	0.98	12.34	1.38	< 0.05
	Symptomatic infection	1.11	0.43	12.34	1.38	< 0.001

Table (3): Mean levels of IL10 among patients with HBV and HCV infections. This showed that IL10 was significant increase in asymptomatic chronic HBV and HCV in comparison to control group (P value<0.05) and highly significant increases in symptomatic chronic HCV and HBV infection in comparison to control group (P value <0.05).

Infection		IL-10		Control		P value
		Means	SD	Means	SD	
Patients with HBS chronic hepatitis	Asymptomatic infection	44.95	5.43	6.2	0.92	< 0.05
	Symptomatic infection	115.12	414.38	6.2	0.92	< 0.001
Patients with HCV chronic hepatitis	Asymptomatic infection	52.36	7.84	6.2	0.92	< 0.05
	Symptomatic infection	124.50	16.13	6.2	0.92	< 0.001

Table (4): the frequency of HCV according to its genotyping

HCV Genotype by Real time PCR technique	Studied groups		HCV positive		HCV negative		Total	
	HCV RNA positive	1a	6	33.33	0	0	6	33.33
		1b	2	11.11	0	0	2	11.11
		4	7	38.89	0	0	7	38.89
		Mixed(1a+4)	2	11.11	0	0	2	11.11
		Mixed (1b+4)	1	5.56	0	0	1	5.56
		Total	18	100	0	0	18	100
	Control	Any or all type	0	0	14	100	14	100

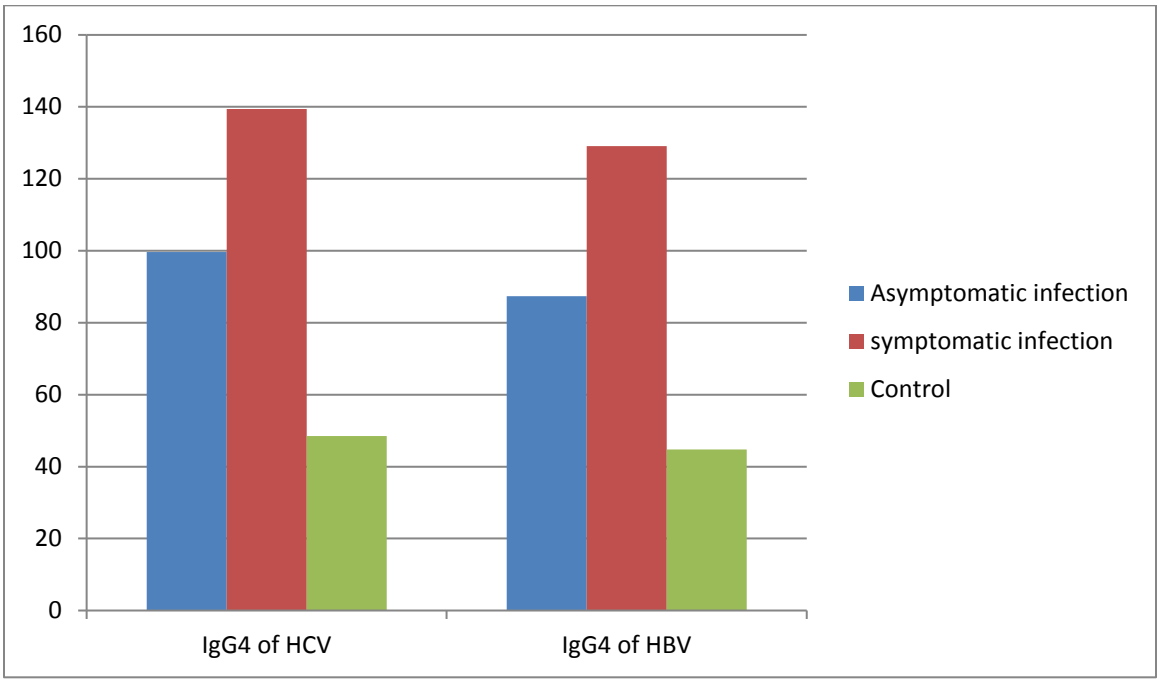

Figure (2): the mean IgG4 level in asymptomatic and symptomatic HCV and HBV infections

Discussion

Carey had stated that ELISA was accurate serological marker for diagnosis of HCV infections but it still gave false positive and false negative results(28). So the wide discrepancy could be attributed to the fact that HCV might be founded in peripheral blood mononuclear cells and not in serum or plasma to be detected serologically (29) in addition to that the spontaneous viral clearance might occur in twenty percent of individual exposed to the virus (30).

As it was shown in this study that the IL4 (table 2) was decreased and IL10 (table 3) was increased in symptomatic than in asymptomatic chronic HBV and HCV infection, so these might lead to inhibition of activated macrophages and cell-mediated immunity (Th1) and subsequently lead to potent down-regulation of IFN-γ by Th1 cells and inhibits the immune response to viral infection that finally resulted in imbalance in Th1 and Th2 cytokines to be concerned as an significant part in the pathogenesis of chronic hepatitis (31)with subsequent change in liver enzymes and aggravating the disease symptoms (32). This was consistent with (31). This might be due to type of intrahepatic infiltrating T cells which could be Th1 cells that were unable to secrete IL-4 (33), so this might reflect disease severity. It was noteworthy that there was a correlation between T cell response and a clinically benign course of the liver diseases and eradication of the virus. As the assessment parameter nowadays was the histopathological examination which was invasive laboratory technique and as there was significant reduction of IL-4 occurred in symptomatic infections, so this parameter might indirectly reflect the pathological picture in these diseases and might be used as a laboratory parameter to indirectly assess liver damage by serum examination instead of histopathological examination or when the later technique was indicated to be repeated in future for many times to assess treatment

efficacy. Further studies would be recommended to confirm the true histopathological status in relation to serum levels of these two parameter together with large sample size.
As Th2 was anticipated to be down regulated in this study through a decrease production of IL4 (table 2), so the highly significant production of IL10 may be from cells other than Th2 e.g. numerous cell forms in liver, containing hepatocytes, hepatic stellate cells, sinusoidal endothelial cells, Kupffer cells and liver-associated lymphocytes which had anti-inflammatory action through the inhibition of IL-6, IL-8, IL-12, and TNF-α synthesis by activated macrophage and interferon-γ by T cells (35). In addition to that inhibition of activated macrophages, which played a crucial role in the homeostatic control of innate immune reactions and cell-mediated immunity might lead to potent down-regulation of the production of IFN-γ by Th1 cells and inhibition of the immune response to viral infection (36), so it might influence HCV and HBV infection susceptibility(37). The significant reduction in IL10 production in those patients with asymptomatic HBV and HCV infection in comparison to symptomatic HBV and HCV might be responsible for reduction of symptoms and a better enhancement of immune response against virus, so this might favor a forceful CD4+ and CD8+ T-cell response with a tendency to rise in Th1 cytokine profile and this seem to be accountable for recovery from these chronic infections(38). On the other hand, patients who progress to symptomatic chronic infection and showed a prime Th2 response could down regulates the Th1 response and therefore favors persistent HCV infection. It had been reported that the IL-10 gene promoter polymorphisms might occurred during the natural course of HCV infection (39). It had been shown that inter-individual difference in IL-10 production was determined genetically(40). Therefore, there is a prerequisite for larger studies to propose any part of cytokine gene polymorphisms in HCV outcome and in order to orient molecular epidemiological research of IL-10 polymorphisms sites and HCV infection susceptibility in the future.

It is now well documented that therapeutic outcome of antiviral treatment is influenced by the virus genotype as prior knowledge of the genotype before therapy had become an important aspect of therapeutic strategy, because of its predictive value in terms of the response to antiviral therapy. It also provides information as to strain variation and potential association with disease severity. In addition, it is of epidemiologic value because it sheds light on whether prevalent HCV strains are similar to that endemic in a certain region, such as in the Middle East(41).
Table(4): showed that 7 out of 18 (38.89 %) had HCV genotype 4 ,hence it was considered the commonest genotype, followed by HCV genotype 1a (33.33 %), HCV genotype 1b (11.11%), mixed HCV genotype (1a+4)(11.11%) and mixed HCV genotype (1b+4) (5.56%). The mixed infections that had been noted in this study could be attributed to mutations in the viral genome or co-infection of both together (42).Five out of 6 (83.33%) of patients with HCV genotype 1a give history of using hemodialysis , so it was more likely to disseminate in hemodialysis. This was consistent with (43). Infection with two or more different HCV genotypes has been observed in hemodialysis patients (44). Grouping of anti-HCV positive patients in dialysis units might thus increase the risk of acquiring multiple HCV strains. So using PCR technique for grouping of anti-HCV positive patients in relation to HCV genotype might be helpful to prevent HCV genotypes co-infection. The pattern of HCV genotypes encountered in this study was similar to those reported from other countries such as Saudi Arabia and Lebanon, where genotype 4

is the most prevalent (45&46). However, this should not be general to all HCV cases widespread in Iraq because of small size sample. Analysis should be done with a larger population, including hemodialysis patients and blood donors, to determine the prevalent HCV genotype (45). HCV genotype 1a is the most prevalent genotype in Jordanian patients' blood donors and in haemodialysis patients of some Middle Eastern countries including Lebanon, Turkey, Cyprus and Syria. In contrast, HCV genotype 4 was the most prevalent genotype in other Middle Eastern countries including Saudi Arabia, Egypt, Yemen and Bahrain (47).

Fig. (2) showed that there was significantly high IgG4 level in symptomatic infection of both types (P value > 0.05). This probably due to increase in IL-10 that had been found in this study as excessive production of this anti-inflammatory cytokines would triggers an overwhelming expansion of IgG4-producing plasma cells (48&49). It had been shown previously that the serum IgG4 was positivily linked with the increase in peripheral memory T regulatory cells(49) and the up regulation of IL-10 in livers of the patients with IgG4-sclerosing cholangitis was by prominent infiltration of T regulatory cells, so this outcomes suggested that IgG4 did not act as a pathogenic factor, but as an anti-inflammatory element that might worsen the course of disease due to the anti-inflammatory action of IL-10. Based on genetic experiences, acquired and innate immunity, regulatory T or B cells, Th2-dominant immune status, and complement activation through a classical pathway might be complicated in the progress of IgG4-related disease. Although the role of IgG4 remains unclear in IgG4-related disease, IgG4-production was up regulated by IL-10 from T regulatory cells and by B cell activating factor from monocytes/basophils with toll-like receptors/nucleotide-binding oligomerization domain-like receptors stimulation(50). Further studies are necessary to clarify the pathogenic mechanism of IgG4.

Conclusions

It could be concluded that host immune elements are significant in the consequence of HBV and HCV infection. Serum IL4 might be used as a laboratory parameter to indirectly assess liver damage instead of invasive histopathological examination. IL-10 might influence HCV and HBV infections susceptibility due to its anti-inflammatory action. IgG4 might further aggravate the disease course caused by IL-10.

Recommendations

1-Further study are recommended to study IL4 and IL10 gene polymorphisms as they may potentially lead to spontaneous clearance of viral hepatitis infection.
2- Further study with large sample size are indicated.

Conflict of Interests.

There are non-conflicts of interest .

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الخلاصة

الخلفية العلمية: فيروسات التهاب الكبد هي مسببات شائعة للالتهاب الكبد ولها انتشار مختلف في ما بين المرضى ولها خمسة انواع شائعة: فايروس التهاب الكبد نوع A, B, C, D, E, . فايروس التهاب الكبد نوع B, C and D تحدث عن طريق الحقن. فايروس التهاب الكبد نوع E يحدث خاصة لدى النساء الحوامل عن طريق الجهاز الهضمي. الانترلوكين −4 يحمي خلايا الكبد من موت الخلايا المبرمج ويثبط من تكاثر فايروس التهاب الكبد نوع B. التعرض الى مستضدات فايروس التهاب الكبد نوع C يزيد انتاج الانترلوكين −10 عن طريق الخلايا الحبيبية متعددة الاشكال و الخلايا التائية.

هدف الدراسة :لمتابعة اهمية الانترلوكين−4 والانترلوكين−10 بين المرضى الذين يعانون من التهاب الكبد الفايروسي نوع Bو نوع C ولإيجاد معدل الحالات المؤكدة في محافظة بابل وللمقارنة بين معدل تلك النسب والاسباب المحتملة للانتقال وطرق الوقاية.

المواد وطرق العمل: تم اخذ مجموعة مكونة من 18 مريض تعاني من التهاب الكبد الفايروسي نوع Bونوع C لمقارنة الانترلوتكين −4 والانترلوكين −10 وتمت المقارنة مع مجموعة السيطرة المكونة من 14 شخص والذين لا يعانون من مرض ظاهريا في مختبر الصحة العامة/بابل

النتائج: اظهرت النتائج نقص معنوي كبير في الانترلوكين −4 في كلا المجموعتين بالمقارنة الى مجموعة السيطرة بينما كان هنالك زيادة معنوية كبيرة في كلا المجموعتين بالمقارنة مع مجموعة السيطرة.

الاستنتاج:

العوامل المناعية تكون ضرورية جدافي مصير التهاب الكبد نوع Bو نوع C. ومن الممكن استخدام الانترلوكين−4 كمعيار مختبري غير مباشر لتقييم ضرر الكبد بدلا من الفحص النسيجي. الانترلوكين −10 من الممكن ان يزيد الاصابة بالتهاب الكبد نوع Bو نوع C بسبب دوره كعامل مضاد للعوامل الالتهابية. وكذلك الاميونوكلوبين نوع G4 من الممكن ان يزيد من التهاب الكبد نوع Bو نوع C المتسبب ب الانترلوكين−10.

الكلمات الدالة: التهاب الكبد نوع Bو نوعC , الانترلوكين −4, الانترلوكين−10