Original Article

Chronic Liver Diseases

Beyond the Liver ! Extra Hepatic Manifestations: Assessment of Frequency and Risk Factors among Hepatitis B & C related Chronic Liver Diseases

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ABSTRACT

Objectives: The study aimed to determine the frequency and risk factors for Extra Hepatic Manifestations among patients with Hepatitis B and C related Chronic Liver Diseases.

Study Design: Cross Sectional Study

Place and Duration of Study: This Study is conducted at the Department of Medicine (Both indoor & outdoor patients) of Civil Hospital, Karachi from 2012 to 2016.

Materials and Methods: In this study of 548 patients, who were positive for HBV or HCV, fulfill the selection criteria and were suffering from Chronic Hepatitis, Cirrhosis or HCC were examined for Extra Hepatic Manifestations clinically and if required appropriate tests were done to confirm the diagnosis & finding. Frequency and risk factors were determined for extra hepatic manifestations. Test of statistical significance were applied where p value of <0.05 was considered to be statistically significant cut-off.

Results: Majority of patients 432 (78.8%) were HCV Positive and 116 (21.2%) were found to be HBV positive. Overall frequency of extra hepatic manifestations was found to be 54.7 %. Patients with chronic hepatitis C and B. The Extra Hepatic Manifestations of 60.6 % in HCV and 32.8% in HBV respectively. Diabetes Mellitus (DM) is the most common extra hepatic manifestation found in both, chronic HCV (19.0%) and chronic HBV patients (5.2%) whereas hypertension is the second commonest extra hepatic manifestation among HBV patients (12.1%). Disease duration > 5 years, age> 45 years, Viral PCR, Raised ALT and Hepatocellular Carcinoma associated with chronic HCV and HBV were found to be significant risk factors for extra hepatic manifestations.

Conclusion: Extra Hepatic Manifestations are more common in HCV associated liver diseases than HBV. Diabetes and hypertension are the main extra hepatic manifestation among HBV & HCV positive patient. Disease duration > 5 years, age> 45 years, Viral PCR, Raised ALT and HCC associated with chronic HCV and HBV were found to be significant risk factors for Extra Hepatic Manifestation

Key Words: Extra Hepatic Manifestations, Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Hepatocellular Carcinoma

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INTRODUCTION

The most important causes of liver diseases, especially in the developing countries is viral related (HBV and HCV).[1] HBV and HCV have chronically infected over 350 and 185 million people respectively, [2] mainly from third world countries.[3] Hepatitis C is responsible for cirrhosis in 70 – 80 % of cases followed by hepatitis B in 15 % of cases.

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Several extra hepatic manifestations (EHM) aredescribed in the course of hepatitis B & C virus infection. 40 – 74% HBV or HCV infected patients may develop at least one extra hepatic manifestation at some stage in their course of illnes.[4] Diabetes Mellitus, hypertension, dermal manifestations[5], various glomerulonephropathies, cryoglobulinemia[6], thyroid diseases,[7]vasculitis, lymphoproliferative disorders, neuropathies and cardiomyopathies etc are frequently reported.

EHM sometimes may be the preceding clinical symptom in chronic HCV and HBV patients even before manifestation of Liver Disease. The extra hepatic tissues, which contain viruses (HBV and HCV) serve as asource for persistent infection and its reactivation. Various viral proteins expressed during replication of HBV & HCV in extra hepatic tissue itself responsible for EHM. The autoimmunity with accumulation of circulating immune complexes is the

pathogenesis of these infections. Apart from hepatic tropism HCV has also showly mphotropism, which explains many of the EHM.[8] There are various risk factors like advance age, longer duration of disease, age and gender have been described for EHM among chronic HCV and HBV infected patients.

Pakistan is a country with a huge burden of viral related (HCV & HBV) where data on extra hepatic manifestations is scanty. Thus study is designed to

- Determine frequency of extra hepatic manifestations among chronic HCV and HBV patients
- Assessment of various risk factors for extra hepatic manifestation among chronic HCV and HBV patients

MATERIALS AND METHODS

This was a retrospective cross sectional study conducted in the department of medicine, Civil Hospital, Karachi. Sample size was calculated by open api software version 3 taking 50% of a variable and 95% confidence level and 5% confidence limit. Total sample size was required to be 406 patients. However, 548 confirmed cases of chronic hepatitis B and C were retrospectively screened. Chronic hepatitis, Cirrhosis or HCC were confirmed on biochemical, clinical, sonologically and even with histopathological basis wherever required.

Data was analyzed by SPSS Version 16 where appropriate test of statistical significance were applied.

Inclusion Criteria: All patients positive for HBV & HCV.

Exclusion Criteria: All Patients of Acute Viral Hepatitis with B & C.

RESULTS

Out of 548 patients, 432 (78.8%) were chronic HCV and 116 (21.2%) were chronic HBV. 352 patients (64.23%) were male and 196 (35.77%) were female. Age distribution of patients is mentioned in Table 01. Demographic profiles of both HCV and HBV related chronic hepatitis have shown in Table 02.

Table No.1: Age Distribution of Patients

Years	No.	%age
18 to 30	92	16.79
31 to 45	208	37.96
46 to 60	188	34.31
61 & above	60	10.95

(Average Age: 44 Years) n= 548

EHM were revealed in 300 (54.7 %) patients. 262 (60.6 %) patients with chronic HCV had different extra hepatic manifestations. 38 (32.8%) patients with chronic HBV had EHM. Various EHM among both chronic HBV and HCV are highlighted in Table 03. 88 (16.1%) patients had DM as an EHM in both chronic HCV and HBV. 14 (12.1%) patients with chronic HBV hepatitis had HTN is the second most commonest EHM. The risk factors for EHM in chronic HCV patients were age > 45 years (odd ratio = 1.69, p = 0.008), disease duration > 5 years (odd ratio = 1.54, p = 0.03) and Hepatocellular carcinoma (odd ratio = 1.55, p = 0.036), Viral PCR (odd ratio = 1.97, p = 0.001), Raised ALT Level (odd ratio = 1.17, p = 0.031)as shown in Table 04. The risk factors for EHM in chronic HCB patients were disease duration > 5 years (odd ratio = 2.41, p = 0.032) and HCC (odd ratio = 2.28, p = .039), Viral PCR (odd ratio = 0.332, p = 0.015), Raised ALT Level (odd ratio = 4.47, p = 0.002) as shown in Table 05.

Table No.2: Demographic profile of chronic (HBV & HCV) patients with Extra Hepatic Manifestation (EHM)

Demographic parameters n= 548		Number of patients	Frequency
Chronic HCC Related Demographics N=432 (78.8%)			
Age:	>45	248	57.4%
	<45	184	42.5%
Gender	Male	255	59.0%
	Female	177	41.0 %
EHM		262	60.6%
Chronic HBV Related Demographics N=116 (21.2%)			
Age	>45	70	60.3%
	<45	46	39.65%
Gender	Male	73	62.93%
	Female	43	37.0%
EHM		38	32.8%

Table No.3: Extra Hepatic Manifestations among Chronic HBV and HCV

Manifestations	HBV +ive n=116 (21.2%)		HCV +ive n=432 (78.8%)		Total n=548	
	No.	%	No.	%	No.	%
DM	06	5.2	82	19.0	88	16.1
HTN	14	12.1	42	9.7	56	10.2
Lichen Planus	02	1.7	38	8.8	40	7.3
Renal Diseases	06	5.2	10	2.3	16	2.9
Cryoglobulinemia	00	00	06	1.4	06	1.1
Hypothyroidism	00	00	10	2.3	10	1.8
Hyperthyroidism	00	00	06	1.4	06	1.1
Thyroiditis	00	00	02	0.5	02	0.4
RA	00	00	06	1.4	06	1.1
CMP	00	00	16	3.7	16	2.9
Lymphoprolif-erative Disorder	00	00	04	0.9	04	0.7
Sensory Neuropathy	00	00	10	2.3	10	1.8
Purpura	02	1.7	14	3.2	16	2.9
Sialadenitis	08	6.9	16	3.7	24	4.4
Total	38	32.8	262	60.6	300	54.7

Table No.4: Risk factors for Extra Hepatic Manifestations (EHM) among Chronic HCV patients (Univariate Analysis)

Variables		EHM n=432		Odd ratio CI (95%)	Relative RiskCI (95%)	p-Value
		No.	%			
Age	>45 248	152	61.29	1.69 (1.12-2.53)	1.26 (1.05-1.53)	0.008*
	<45 184	89	43.36			
Gender	Male 255	140	54.9	1.31 (0.88-1.97)	1.14 (0.94-1.39)	0.17
	Female 177	85	48.02			
Duration of Disease	> 5 years 272	138	50.7	1.54 (1.02-2.34)	1.268 (1.01-1.61)	0.03*
	< 5 years 160	64	40			
HCC	With HCC 159	89	55.97	1.55 (1.02-2.34)	1.24 (1.01-1.50)	0.036*
	Without HCC 273	123	45.05			
HCV RNA	Detectable 260	151	58.05	1.97 (1.30-2.97)	1.47 (0.14-1.75)	0.001*
	Undetectable 172	71	41.27			
ALT Level	Raised 281	201	71.5	1.61 (1.03-2.49)	1.17 (1.01-1.35)	0.031*
	Normal 151	92	60.92			

* **Statistically Significant**

Table No.5: Risk factors for Extra Hepatic Manifestations (EHM) among Chronic HBV patients (Univariate Analysis)

Variables		EHM n=116		Odd ratio CI (95%)	Relative RiskCI (95%)	p-Value
		No.	%			
Age	>45 70	42	19.44	1.78 (0.78-4.08)	1.31 (0.89-1.99)	0.18
	<45 46	21	45			
Gender	Male 73	35	30.17	0.72 (0.31-1.66)	0.859 (0.59-1.29)	0.41
	Female 43	24	55.81			
Duration of Disease	> 5 years 76	45	59.21	2.41 (1.02-5.7)	1.57 (1.01-2.26)	0.032*
	< 5 years 40	15	37.5			
HCC	With HCC 51	30	58.8	2.28 (1.01-5.19)	1.52 (1.00-2.28)	0.039*
	Without HCC 65	25	38.46			
HBV DNA	Detectable 80	43	53.7	0.332 (0.12-0.88)	0.69 (0.51-0.95)	0.015*
	Undetectable 36	28	77.7			
ALT Level	Raised 90	56	66.2	4.47 (1.56-13.28)	2.31 (1.24-5.19)	0.002*
	Normal 26	19	73.33			

* **Statistically Significant**

DISCUSSION

Patients with chronic HBV & HCV infections had more Diabetes mellitus (DM) than in the general population.[9, 10] HCV independent to underlying liver disease is now considered as a well established risk factor for DM. Earlier studies reported strong association of DM with advanced liver fibrosis among HCV patients.[11, 12] DM is prevalent in cirrhotics where 25% were due to underlying HCV and 19% had alcoholic liver disease. This fact is paralleled to our results (19%). In patients having chronic HCV infections with diabetes, the causative factor is increase insulin resistance rather than presence pancreatic anti-islet antibodies.

Hypertension in these infections has been observed to prevail in around 10% to 12.5% while0.1% to 25% of the sufferers have some variant of glomerulonephritis.[13,14] Brzosko and colleagues while depicting HBV connection in the pathogenesis of glomerulonephritis documented an incidence of 34.6% in diverse forms of glomerular disease.[15] HBV and HCV infections are linked tovarious types of glomerulonephritis, where apparently membranous glomerulonephritis (MGN) being the commonest entity.[16] This particular study derived the frequency of glomerular diseases to be 2.3% to 5.2% in HCV and HBV infection respectively. HBV and HCV allied MGN, by and large presents as Nephrotic syndrome having proteinuria, chronic renal failure. The asymptomatic cases imperatively present with hypertension.[17,18]

immunoglobulins precipitation (reversible) in a cold environment has been linked to HBV and HCV. Cryoglobulins are classified into three types where; type II (Monoclonal IgM and Polyclonal IgG) and type III (Polyclonal IgM and Monoclonal IgG) are known to cause essential cryoglobulinemia present in chronic HBV and HCV infection. Cryoglobulinemia is prevalent in approximately 0-15% of cases.[19,20] This study observed purpuraseconded by arthralgia in 1.4% of patients associated with chronic HCV infection, as commonest presenting features.

The frequency of lichen planus in chronic HBV and HCV infections were 1.7% to 8.8% respectively.[21]An earlier study reported a high prevalence of oral lichen in patients with HBsAgpositivity.[22] Lichen planus typically involves the oral mucosa, tongue, and skin.

These are papular lesions that resemble lichen. In lichen epidermis may be normal, hypertrophic, or atrophic. The deeper basal layer of skin shows vesicles due to degeneration or liquefaction.[23]

The direct link of thyroid diseases with HCV infection is imprecise. Hypothyroidism (2.3%) is more common than hyperthyroidism (1.4%) in patients with HCV infection.[24, 25] Pampana A, et al have reported in their study 13% HCV patients had hypothyroidism where thyroid antibodies were found in 25% patients.[26, 27]

HCV may initiate plaque formation and increases the risk of atherosclerosis as evidenced in an earlier study.[28] HCV with active viral replication increases the risk of carotid atherosclerosis in some part of the world.[29]The pro-atherogenic cytokines in HCV have been liked with plaque instability, suggestits role for increase risk of cerebrovascular diseases. Recently patients with HCV or having co infection (HCV-HIV) validated the connection between carotid atherosclerosis and HCV infection.[30]The 3.7% cardiovascular disease in this study correlated with HCV infection.

Rheumatological manifestations have also been described in chronic HCV infection where 74% of patients had arthralgia or arthritis. Fatigue (1.4%) is the frequently reportedproblem with fibromyalgia in some caseshave been reported.[31]Cryoglobulinemia and polyarteritisnodosahave been described in vasculitis associated with HCV. 20-50% of HCV infected patients had shown various auto antibodies in their serum likeantinuclear antibodies (ANA), RF, cryoglobulins, anticardiolipin antibodies,, anti-smooth muscle, anti-liver kidney microsomal antibodies (Anti LKML) and anti-thyroid peroxidase. [32-34]

Non-Hodgkin lymphoma (NHL) is a frequently reported association with HCV infection.[35] Clonal expansion of B lymphocyte along with environmental and genetic events with chronic HCV has been proposed mechanism of NHL.[36] Program cell death (apoptosis) of lymphocyte infected with HCV which leads to over expression of the bc12 oncogene, with anadditional mutation (myc oncogene) is an another explanation of NLH.[37, 38]

Advance liver fibrosis and old age was found to be significant in earlier reported study among chronic HCV patients.[39] This study has shown advance age, longer duration of disease, raised ALT, Viral PCR and associated hepatocellular carcinoma as significant risk factors for EHM among chronic HCV patients. Longer duration of disease, raised ALT, Viral PCR and hepatocellular carcinoma was found to significant risk factors for EHM among chronic HBV patients.Cacoub P et al in their study contrasted with our study where above risk factors were found to be in significant for EHM among chronic HBV patients. [40]

CONCLUSION

Extra hepatic manifestations are more common in HCV associated liver diseases than HBV. DM & HTN are the main EHM reported in our study among HBV & HCV positive patients. Disease duration > 5 years, age> 45 years, Viral PCR, Raised ALTand HCC associated with chronic HCV and HBV was found to be significant risk factors for Extra Hepatic Manifestation.

Conflict of Interest: The study has no conflict of interest to declare by any author.

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