MEDICAL CHANNEL

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ASSOCIATION OF HEPETITIS B & C VIRUS INFECTION IN NON HODGKIN'S LYMPHOMA: A CASE CONTROL STUDY

1. **SHAIKH KHALID MUHAMMAD**
2. **BASHIR AHMED SHAIKH**
3. **KOURO MAL GURBAKHSHANI**
4. **SHAFIQUE REHMAN SHAH**
5. **MUHAMMAD ASLAM SOOMRO**

1. ***Consultant Physician,*** Chandka Medical College & Hospital Larkana.
2. ***Associate Professor of Medicine,*** Chandka Medical College & Hospital Larkana.
3. ***Assistant Professor of Medicine,*** Chandka Medical College & Hospital Larkana.
4. ***Senior Registrar, Chandka Medical*** College & Hospital Larkana
5. ***Assistant Professor of Medicine,*** Chandka Medical College & Hospital Larkana

Correspondence:
DR. SHAIKH KHALID MUHAMMAD
M.B, B.S, FCPS (MEDICINE)
Consultant Physician
E-mail:
sheikhkhalid_doctor@hotmail.com
Cell. No: + 92 333 2619052

ABSTRACT

Objectives: To determine the association between hepatitis B virus (HBV) and hepatitis C virus (HCV) infection and Non Hodgkin's Lymphoma (NHL).
Duration & Design: This 2 year observational and analytical, case control study was started on 1st January 2009 at C.M.C Larkana, after approval of ethical review committee.
Methods & Materials: After informed written consent, blood samples from 361 NHL cases and 1444 age and sex matched controls (2 groups) meeting our selection criteria, were sent for detection of HBsAg and Anti-HCV Ab on 3rd generation ELISA. Pearson's chi-square test was applied to compare HBsAg and Anti-HCV Ab seropositivity in cases and controls and odd ratios were computed using SPSS version 10.
Results: 69 (19.1%) of cases, 55 (7.6%) controls in group 1(1st Degree Relatives) and 60 (8.3%) controls in group 2 (Non Hematological Malignancy) were HBsAg positive, with odd ratios of 2.86 (95% CI; 1.96 – 4.19) for control group 1 and 2.60 (95% CI; 1.79 – 3.78) for control group 2. Beside, 52 (14.4%) of cases, 53 (7.3%) subjects in control group 1and 58 (8.0%) in control group 2 were Anti-HCV Ab positive, with odd ratios of 2.12 (95% CI; 1.41 – 3.18) for control group 1 and 1.92 (95% CI; 1.29 – 2.86) for control group 2. P value was 0.000 for both.
Conclusion: HBsAg and Anti-HCV Ab seropositivity is associated with 2-3 times risk of development of NHL.

Key Words: HBV, HBsAg, HCV, Anti-HCV Ab, ELISA, Association, NHL.

INTRODUCTION

Globally an estimated 350 million persons are infected with HBV and 170 million with HCV and around 3-4 million are newly infected each year with HCV.[1,2] Currently the prevalence of HBV and HCV in Pakistan is 2-5% and 4-7% respectively.[3] Both are hepatotropic virus, causing chronic hepatitis, Cirrhosis and Hepato-Cellular Carcinoma.[4] HCV and HBV are also lymphotropic and by infecting peripheral mononuclear cells can predispose to lymphoproliferative disorder as Non-Hodgkin Lymphoma (NHL).[5,6] Increased frequency of B-cell clonality, t(14:18), bcl-2 and Bcl-6 gene translocation, STAT3 activation, up-regulation of ERK and p38 MAPK signaling pathways, is seen in patients of NHL infected with HCV.[7-11] There is also correlation between the expression of HBV X-gene encoded X protein (HBx) and inactivation of p53 and that the suppression of p53 function by HBx may lead to abnormal cell division. Persistence and replication of HBV in extra hepatic tissues as lymph nodes and bone marrow further support the causation.[12-14]

The initial evidence of association came from high prevalence or frequency of HBV and HCV infection in patients of NHL as compared to general population, blood donors or controls in various countries.[15-21] Other features that support association of HBV and HCV with NHL are early or young age of onset and higher or advanced stage/grade in infected patients.[21,22] But, the data from Pakistan is controversial and has shown the prevalence of HCV in lymphoproliferative disorder (including NHL) is just 5% as

compared to general population of 4-7%.[23]

There are limited studies conducted in our region on this issue. This was a matter of particular interest for us, given the documented association between non-Hodgkin's lymphoma and hepatitis B and hepatitis C virus infection. So, this case control study was carried out to determine the current frequency of HBV and HCV infection in patients of NHL as compared to other non-hematological malignancies and diseases free relatives of NHL patients.

MATERIAL AND METHODS

This two year case control study was started on 1st January 2009, after the approval of ethical review committee of C.M.C Larkana. All cases and controls were enrolled from Departments of C.M.C Hospital Larkana and LINAR (Larkana Institute of Nuclear Medicine And Radiotherapy) after informed written consent.

Inclusion Criteria

All consecutive biopsy proven, newly diagnosed and treatment naïve cases of NHL of either sex.

Exclusion Criteria

1. Patient not consenting.
2. Previously diagnosed HCV & HBV patient.
3. Exposure to radiations and chemo therapy.
4. Patient receiving treatment for NHL either palliative or curative.
5. Patient who has received or under gone any blood transfusion and major surgical procedure in last six months.
6. Previously diagnosed as a case of medical disorder requiring parenteral medications e.g. Hemophilia, thalessemias, etc.
7. Patient co-infected with Human Immunodeficiency Virus (HIV) or HBV with HDV (delta antigen) and HBV with HCV.
8. Patients suffering from immunodeficiency state and auto immune disorders.

Selection of Cases and Controls

A total of 378 NHL patients were seen during our study duration. Detailed history was taken from all. 5 patients were excluded as they had received blood transfusion or parenteral symptomatic medications or undergone surgical intervention in last 6 months. 1 patient had past history of irradiation exposure was also excluded. 4 HIV and 2HDV infected patients were also excluded from the patients. Remaining 366 treatment naïve cases of NHL were selected for study and labeled as case group.

Two sex and age (± 5 yrs) matched control groups were formed. Control group 1 (n=732) consisted of 2 first degree relatives of each case, that also matched cases by their district of origin (native place). Control group 2 (n=732) consisted of 2 age and sex matched patient suffering from non hematological malignancies admitted in different wards of C.M.C Hospital Larkana and LINAR. Controls in group 2 were also matched for date of admission (? 7 days). Patients of Hepato-cellular carcinoma were excluded from control group 2.

Data Collection

Blood samples from all cases and controls were sent for detection of HBsAg and anti-HCV Ab on 3rd generation ELISA at Pathology Department of C.M.C Hospital, Larkana. For all HBsAg positive cases infection was confirmed by IgG anti-HBcAb. The results were collected and transferred to predesigned performa by principal researchers.

Data Analysis

Data obtained from total of 366 NHL cases and 732 controls in each control group was transferred to SPSS version 10. 5 cases and there age and sex matched controls were excluded (filtered) from data analysis as they were HBV and HCV co-infected. Finally data of 361 controls and 722 controls in each group was analyzed.

HBV and HCV infection was compared by Chi square test in both cases and controls and Odd Ratios with confidence intervals were computed to see any association between HBV and HCV seropositivity and NHL cases. HBsAg and anti-HCV Ab seropositivity rates were compared in both cases and controls in age categories to observe the impact of seropositivity in different age categories. P value of less than 0.05 was taken as statistically significant.

RESULTS

The cases consisted of 213 men (59.0%) and 148 women (41.0%) and their demographic characteristics are summarized in Table 1. The cases and controls were similar with respect to sex and age. HBsAg was positive in 69 of 361 cases (19.1%), as opposed to 55 of 722 patients (7.6%) in control group 1 and 60 of 722 subjects (8.3%) in control group 2. Anti-HCV Ab was positive in 52 of 366 cases (14.4%), as opposed to 53 of 722 patients (7.3%) in control group 1 and 58 of 722 subjects (8.0%) in control group 2. A higher risk of non-Hodgkin's lymphoma was found in HBsAg and anti-HCV Ab positive subjects than in the HBsAg and anti-HCV Ab negative subjects. The odds ratios for HBsAg seropositivity were 2.86 (95%CI; 1.96 – 4.19) versus control group 1 and 2.60 (95%CI; 1.79 – 3.78) versus control group 2 with p value of 0.000 for both. The odds ratios for anti-HCV Ab seropositivity were 2.12 (95%CI; 1.41 – 3.18) versus control group 1 and 1.92 (95%CI; 1.29 – 2.86) versus control group 2 with p vale of 0.000 for both. The association between HBV and HCV infection and non-Hodgkin's lymphoma remained statistically significant with p values of 0.000 for both and mean odd ratios of 2.73 (95%CI; 1.97 – 3.77) and 2.02 (95%CI; 1.42 – 2.87) respectively (Table 2).

The HBsAg-positive rate was consistently higher for non-Hodgkin's lymphoma patients in every age group except 20 to 40age group. Risk of non- Hodgkin's lymphoma was most evident in the younger HBsAg-positive age group. The odds ratios of non-Hodgkin's lymphoma were 5.71 (95%CI; 2.33 – 14.00), 0.66 (95%CI; 0.14 – 3.03), 3.08 (95%CI; 1.83 – 5.17) and 2.53 (95%CI; 1.47 – 4.38) in the < 20year, 20-40 years, 40-60 years > 60 years age groups with p values of 0.000, 0.598, 0.000 and 0.001 respectively (Table 3).

The anti-HCV Ab positive rate was consistently higher for non-Hodgkin's lymphoma patients in every age group. Risk of non-Hodgkin's lymphoma was most evident in < 20years and 40-60 year anti-HCV Ab positive age group. The odds ratios of non-Hodgkin's lymphoma were 2.63 (95%CI; 1.08 – 6.40), 1.37 (95%CI; 0.52 – 3.58), 2.42 (95%CI; 1.43 – 4.12) and 1.59 (95%CI; 0.74 – 3.40) in the < 20year, 20-40 years, 40-60 years > 60 years age groups with p values of 0.029, 0.511, 0.001 and 0.222 respectively (Table 4).

DISCUSSION

In our study, all efforts were made to exclude NHL cases that had exposure of any known risk factor for lymphoma development. After exclusion, total of 366 patients met our selection criteria. 5 cases and their respective controls were filtered during data analysis as the cases were co-infected with HBV and HCV virus. For cases, age and sex matched controls were selected. The advantage

TABLE: NO: 1.
DEMOGRAPHIC PROFILE OF CASES AND CONTROLS

Characteristics	Case(n=361)	Control 1[a] (n=722)	Control 2[b] (n=722)	P values*
AGE (years)				.000
Mean ±SD, y	44.74 ± 20.16y	45.46 ± 19.27y	47.23 ± 18.90y	
Range	70 (4-74)	69 (5-74)	69 (5-74)	
AGE CATEGORY, n (%)				.997
< 20years	46 (12.7%)	96 (13.3%)	93 (12.9%)	
20 – 39 years	84 (23.3%)	169 (23.4%)	171 (23.7%)	
40 – 59 years	102 (28.3%)	198 (27.4%)	202 (27.3%)	
> 60 years	129 (35.7%)	259 (35.9%)	261 (36.1%)	
GENDER				1.000
Males	213 (59.0%)	426 (59.0%)	426 (59.0%)	
Females	148 (41.0%)	296 (41.0%)	296 (41.0%)	
HBV/HCV SEROPOSITIVITY				.000
HBV POSITIVE	69 (19.1%)	55 (7.6%)	60 (8.3%)	
HCV POSITIVE	52 (14.4%)	53 (7.3%)	58 (8.0%)	
BOTH NEGATIVE	240 (66.5%)	614 (85.1%)	604 (83.7%)	

a. Control group 1= age and sex matched 1st degree relatives.

b. Control group 2= age and sex patients of non hematological malignancies.

*Pearson Chi – Square. (2-sided) Significance.

TABLE: NO: 2.
ODD RISK AND P VALUES FOR ASSOCIATION OF HBV & HCV AND NHL IN CASE AND CONTROLS

CHARACTERISTIC	CONTROL 1	CONTROL 2	CONTROL (1+2)
	OR[a] 95%CI	OR[b] 95%CI	OR[c] 95%CI
HBsAg			
POSITIVE	2.86 (1.96 – 4.19)	2.60 (1.79 – 3.78)	2.73 (1.97 – 3.77)
NEGATIVE	1.00	1.00	1.00
Anti-HCV Ab			
POSITIVE	2.12 (1.41 – 3.18)	1.92 (1.29 – 2.86)	2.02 (1.42 – 2.87)
NEGATIVE	1.00	1.00	1.00
P values[d]	.000	.000	.000

a. Risk of NHL taking control group 1 as reference
b. Risk of NHL taking control group 2 as reference
c. Risk of NHL taking control group 1 & 2 as reference
d. Pearson Chi – Square. (2-sided) Significance

in selecting 1st degree relatives as control group 1 was that, the relative belonged to same locality of origin, plus environmental factors and genetic makeup was supposed to be nearest to cases as compared to any other group of controls. Control group 2 consists of non hematological malignancy

Our study found statistically significant (p=.000) odd ratios for HBV and HCV in NHL cases. The mean odds ratios were 2.73 (95%CI; 1.97 – 3.77) for HBV and 2.02 (95%CI; 1.42 – 2.87) for HCV respectively. So, we can assume that HBV and HCV infected patients are 2 to 3 times more likely to develop NHL as compared to HBV and HCV non-infected patients. Beside HBV and HCV infected patients are at more risk to develop NHL at young age < 20y with odds of 5.71 (95%CI; 2.33 – 14.00) and 2.63 (95%CI; 1.08 – 6.40) respectively.

Park et al. in 2008 at South Korea assessed the association of HBV and HCV with NHL. They compared their results with age and sex matched controls. The prevalence of HBV was found to be 15.1% as compared to 8.1% in controls and prevalence of HCV

TABLE: NO: 3.
HBsAg POSITIVE RATES OF CASES AND CONTROLS ACCORDING TO AGE GROUPS WITH ODD RATIOS AND P VALUES

CATEGORY	**<20yrs**	**20-40yrs**	**40-60yrs**	**>60yrs**
CASES				
n	12/46	2/84	31/102	24/129
%	26.08%	2.38%	30.39%	18.60%
CONTROL 1				
n	5/96	6/169	24/198	20/259
%	5.20%	3.55%	12.12%	7.72%
OR[a]	6.42	.663	3.16	2.73
95%CI	(2.10 – 19.59)	(0.13 – 3.35)	(1.73 – 5.76)	(1.44 – 5.16)
P values[b]	.000[c]	.617	.000[c]	.001[c]
CONTROL 2				
n	6/93	6/171	25/197	23/261
%	6.45%	3.50%	12.69%	8.81%
OR[d]	5.11	.671	3.00	2.36
95%CI	(1.77 – 14.72)	(0.13 – 3.39)	(1.65 – 5.44)	(1.27 – 4.38)
P values[b]	.001[c]	.627	.000[c]	.005[c]
CONTROL 1&2				
n	11/189	12/340	49/395	43/520
%	5.82%	3.52%	12.40%	8.81%
OR[e]	5.71	.667	3.08	2.53
95%CI	(2.33 – 14.00)	(0.14 – 3.03)	(1.83 – 5.17)	(1.47 – 4.38)
P value[b]	.000[c]	.598	.000[c]	.001[c]

a. Risks of non-Hodgkin's lymphoma among HBsAg-positive patients within specified age groups using control groups 1 as reference groups.
b. Pearson Chi – Square. (2-sided) Significance.
c. Statistically significant ($p < .05$).
d. Risks of non-Hodgkin's lymphoma among HBsAg-positive patients within specified age groups using control groups 2 as reference groups.
e. Risks of non-Hodgkin's lymphoma among HBsAg-positive patients within specified age groups using both control groups 1 and 2 as reference groups

was found to be 2.1% as compared to 3% in controls. He concluded that it is HBV and not HCV, which is associated with NHL.[18]
El-Sayed GM et al. in 2006 at Egypt searched for HCV and HBV genomes and antigens in the malignant lymphoma tissues as well as their sero prevalence. They concluded that their results confirm the presence of HBV and HCV antigens and viral sequences in the involved LNs of NHL patients both viruses may be associated with development of NHL.[17]
Mehdi SR et al. in 2006 at Saudi Arabia followed 555 male patients with NHL and investigated them for prevalence of HBV and HCV infection as compared to blood donors. The prevalence was found to be 11.2% and 16.1% for HBV and HCV respectively ($p<.001$). They conclude that background prevalence of HBV definitely affect the rate of NHL, while HCV infection in NHL was independent of background prevalence, beside, HBV was more prevalent in 3rd and 4th decade.[15]
Researchers observed similar results in USA and China.[20,21] Spinelli et al. at Canada, Takeshita et al. at Japan and Marcucci et al. at Italy reconfirmed the findings seen in USA and China.[16,19,24]
The above discussion based on the international literature has showed that Hepatitis B and Hepatitis C are associated with risk of development of Non Hodgkin Lymphoma. Despite that these two monsters are also very common in our region and country, there are very few studies available exploring the issue. The current trend of both these disorders is on remarkable increase; still we are neglecting this issue.

CONCLUSIONS

1. HBV and HCV infection are associated with risk of development of NHL.
2. HBV and HCV infected patients are 2-3 time more likely to develop NHL than non-infected patients and infected subjects are likely to develop NHL at young ages.

RECOMMENDATIONS

1. Our study results are an eye opener for health policy makers.

TABLE: NO: 4.
Anti-HCV Ab POSITIVE RATES OF CASES AND CONTROLS ACCORDING TO AGE GROUPS WITH ODD RATIOS AND P VALUES

CATEGORY CASES	<20yrs	20-40yrs	40-60yrs	>60yrs
n	9/46	6/84	27/102	10/129
%	19.56%	7.14%	26.47%	7.75%
CONTROL 1				
n	7/96	9/169	25/198	12/259
%	7.29%	5.32%	12.62%	4.63%
OR[a]	3.09	1.36	2.49	1.72
95%CI	(1.07 – 8.92)	(0.47 – 3.97)	(1.35 – 4.57)	(0.72 – 4.10)
P values[b]	.003[c]	.564	.003[c]	.214
CONTROL 2				
n	9/93	9/171	26/197	14/261
%	9.67%	5.26%	13.19%	5.36%
OR[d]	2.27	1.38	2.36	1.48
95%CI	(.83 – 6.18)	(0.47 – 4.02)	(1.29 – 4.32)	(0.64 – 3.43)
P values[b]	.102	.549	.004[c]	.356
CONTROL 1&2				
n	16/189	18/340	51/395	26/520
%	8.46%	5.29%	12.91%	5.0%
OR[e]	2.63	1.37	2.42	1.59
95%CI	(1.08 – 6.40)	(0.52 – 3.58)	(1.43 – 4.12)	(0.74 – 3.40)
P values[b]	.029[c]	.511	.001[c]	.222

a. Risks of non-Hodgkin's lymphoma among HBsAg-positive patients within specified age groups using control groups 1 as reference groups.
b. Pearson Chi – Square. (2-sided) Significance.
c. Statistically significant ($p < .05$).
d. Risks of non-Hodgkin's lymphoma among HBsAg-positive patients within specified age groups using control groups 2 as reference groups.
e. Risks of non-Hodgkin's lymphoma among HBsAg-positive patients within specified age groups using both control groups 1 and 2 as reference groups

If neglected, we may be facing an epidemic of NHL in near future. So, all possible measure should be taken to combat this combined epidemic.

2. The results of our study also provide a strong rationale from where other studies could build their hypothesis and massive epidemiological studies conducted to assess the possible pathogenesis and associated risk factors.

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