

Case-control study of non-Hodgkin's lymphoma and hepatitis C virus infection in Egypt

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Background Chronic infection with hepatitis C virus (HCV) has been associated in some studies with increased risk for B-cell non-Hodgkin's lymphoma (NHL). To assess this further, we conducted a case-control study in Egypt, where HCV prevalence is extremely high.

Methods Cases with B-cell NHL ($N = 227$) were recruited from the National Cancer Institute of Cairo University, a major referral centre. Controls ($N = 227$) were patients with fractures being treated at the Kasr El-Aini Orthopaedic Hospital, from the same referral base as the cases, and were frequency-matched by gender, rural versus urban birthplace, and age. Subjects were interviewed about their medical history and possible risk factors, and blood samples were collected for HCV diagnostic tests. Anti-HCV and HCV RNA were determined by enzyme-linked immunoassay and reverse transcription-polymerase chain reaction, respectively. Odds ratios (OR) and 95% CI were calculated from logistic regression models.

Results Overall, 40% of subjects were anti-HCV positive and 28% had HCV RNA. There was a statistically significant unadjusted association of HCV RNA with NHL (OR = 2.3, 95% CI: 1.5, 3.5), which differed slightly by gender (males: OR = 2.1, 95% CI: 1.2, 3.7 versus females: OR = 2.5, 95% CI: 1.3, 4.8). Anti-HCV without HCV RNA was not associated with case status (OR = 0.9, 95% CI: 0.5, 1.6). After adjustment for age, gender, rural versus urban birthplace, and rural versus urban current residence, the association of HCV RNA with the risk of NHL remained statistically significant (OR = 2.9, 95% CI: 1.9, 4.5).

Conclusions These data support the hypothesis that NHL is a malignant outcome of chronic HCV infection.

Keywords Hepatitis C, lymphoma, non-Hodgkin, Egypt, case-control studies

The World Health Organization (WHO) estimates that 170 million people are infected with hepatitis C virus (HCV).¹ An estimated 12–15% of Egyptians, or 8–10 million people, have serological evidence of HCV infection, with higher rates in older

age groups and residents of rural areas in Lower and Middle Egypt.² There is compelling evidence for a large-scale iatrogenic transmission of HCV during a parenteral anti-schistosomal treatment campaign carried out from the 1920s through the 1980s.² Continued transmission in Egypt has been associated with transfusion of unscreened blood; invasive medical procedures, including Caesarean section and abortion; injections by informal health care providers;³ and haemodialysis.⁴

Since its identification, HCV has been added to the roster of tumour-associated viruses because of its role in hepatocarcinogenesis. It has also been linked to upwards of 28 extra-hepatic disease manifestations, chiefly autoimmune in nature. However, some of these reports are inconclusive, and it remains

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to be confirmed that HCV is causally associated with all but a few conditions.⁵

One of the extrahepatic diseases in which HCV has been implicated is B-cell non-Hodgkin's lymphoma (NHL). HCV-associated lymphomas have been observed, but whether they are caused by HCV remains to be shown definitively. There is a suggestion that some B-cell NHL associated with HCV arise from clonal expansion of B-cells with particular immunoglobulin gene rearrangements specific for the E2 protein of the HCV envelope,^{6,7} which is consistent with the hypothesis that lymphomas develop when B cells proliferate in response to antigen.⁶ However, no biological mechanism of HCV-associated lymphomagenesis has been definitively elucidated.

Most of the studies reported to date that failed to find an association of HCV with NHL were conducted in areas where the prevalence of HCV was extremely low, leaving open the possibility that such an association actually exists but could not be detected because neither cases nor controls had adequate opportunity for exposure. Working in a population with high prevalence of HCV allowed us to conduct a case-control study with adequate statistical power to assess the question of whether there is an association of chronic HCV infection with NHL.

Materials and Methods

Case population

Cases with B-cell NHL were recruited between October 1999 and January 2003 from patients attending an outpatient clinic at the Egyptian National Cancer Institute, a major referral centre affiliated to Cairo University. Case patients were eligible to participate if they were over the age of 17, first diagnosed with cancer ≤ 6 months prior to interview, and physically and mentally capable of understanding and completing the interview.

Some participants were new patients who were undergoing tests to establish a diagnosis, and some were returning patients who were about to initiate or were already undergoing treatment; all were recruited within 6 months of initial diagnosis. *Provisional cases* were those whose lab slips indicated a diagnosis or suspicion of NHL. Their classification as a case was subject to change after confirmation of their diagnoses through pathology data and medical records review. Subjects whose diagnoses were not located or finalized during record review, or who were found to have a diagnosis other than an NHL, were dropped from the study.

Selection of controls

Control subjects free from cancer were sampled by gender and birthplace from among all patients of the Kasr El Aini Faculty of Medicine Orthopaedic Hospital in Cairo, Egypt. They were frequency-matched to the case group by rural versus urban birthplace, gender, and 5-year age category. The rationale for selecting orthopaedic patients, all of whom were being treated for fractures, was: (1) they would be representative of the source population of the cases by region, since both hospitals draw patients from the same area and (2) they would be representative of the general population with respect to HCV infection, since HCV positivity and fracture are exceedingly

likely to be independent. Potential controls had to be ≥ 18 years old, and physically and mentally capable of participating.

Interview procedures

Ethical review boards at all involved institutions approved the study. Written or witnessed oral informed consent was obtained from all participants before enrolment. Trained research assistants administered a standardized Arabic-language questionnaire in a face-to-face interview that lasted 30 minutes. The questionnaire asked about residence, employment, and smoking histories; exposures to pesticides and other industrial or agricultural substances; social and educational factors; and medical history. On completion of the interview, a blood specimen was collected. There was no further follow-up with the study subjects.

Laboratory assays

Within 6 hours of collection, the blood was separated and the serum divided into aliquots and stored at -80°C . Samples were later thawed and tested for anti-HCV antibody by Abbott HCV enzyme-linked immunoassay (EIA) 3.0 (Abbott Park, IL, USA) according to the manufacturer's instructions. Samples were initially tested for HCV RNA by direct nested reverse transcription-polymerase chain reaction (RT-PCR) as described previously.⁸ A positive result by the direct RT-PCR method was considered truly positive, and no further investigation was done. A sample that was negative by both direct RT-PCR and EIA was considered negative. However, all samples that tested negative by direct nested RT-PCR and positive by EIA were re-tested by conventional RT-PCR, which differed from direct RT-PCR in that it included an RNA purification step.

In all cases where formalin-fixed tissue from NHL cases was available at the Egyptian National Cancer Institute, immunophenotyping for B- and T-cell markers was performed at the Department of Pathology. Identification of B- and T-cell surface markers was carried out using pan-B (CD-20) and pan-T (CD-45) monoclonal antibodies with the DAKO EnVision System (Code No. K4006, DAKO, Carpinteria, CA, USA). This is a two-step indirect staining technique similar to the avidin-biotin complex method. The test was performed according to the manufacturer's instructions in the package insert. Cases that tested positive for the B-cell marker were retained, while those positive for the T-cell marker were dropped from analysis, regardless of previous classification based on histological examination of haematoxylin and eosin-stained slides.

Statistical analyses

Environmental exposures from the questionnaire were examined as dichotomous, 'ever/never' variables, and age (in 2000) was included as a continuous variable. Region of current residence was categorized as 'Upper Egypt and Deserts' (hereafter referred to as 'Upper Egypt') and 'Lower Egypt'. This geographical distinction should not be confused with the distinction between rural and urban, which is based on participants' self-reported birth in a rural or urban area and was used as a matching criterion. Rural and urban areas might be located in either Upper or Lower Egypt.

Characteristics of cases and controls in the entire sample and in males and females were compared either by Pearson's χ^2 test

(for categorical variables) or by a t-test (for continuous variables). Point estimates and exact 95% CI were calculated for unadjusted unmatched odds ratios (OR) using PCR-negative participants as the reference group in the first case, regardless of EIA results, and those negative for HCV by both PCR and EIA as the reference group for the joint analysis of EIA and PCR. Because both HCV infection and NHL occur more frequently in males than in females, analyses were stratified to determine if any observed HCV-NHL association differed by gender.

Adjusted OR and 95% CI were obtained by standard logistic regression. Potential confounders were identified as variables whose inclusion in a logistic regression model resulted in a change of $\geq 5\%$ in the baseline OR.⁹ Final multivariate logistic regression models included HCV RNA, age, gender, urban versus rural birthplace, and the variables identified as confounders from the preliminary analyses. Reported *P*-values were based on two-tailed tests. All statistical analyses were performed using SAS, version 9.0 (Cary, NC).

Results

In all 986 provisional NHL cases at the National Cancer Institute patients were asked to participate. In total, 103 (10.4%) of these provisional cases refused participation outright; 345 (35.0%) cases claimed they were too ill or otherwise incapable of participating; and one provisional case was ineligible. Of the 538 provisional cases who participated in the study, 227 (87%) were confirmed as definite cases on record review. Seventy-six per cent (227/299) of the controls participated, so that the final

study population of 454 comprised 227 NHL cases and 227 cancer-free controls from the Kasr el-Aini Orthopaedic Hospital.

Table 1 shows the distribution of demographic and other selected characteristics in cases and controls. Cases and controls were well matched by place of birth (rural versus urban), age, and gender, but controls were more likely overall to reside currently in a rural area ($P < 0.01$). Controls were more likely to be born and to reside in Upper Egypt, regardless of gender ($P < 0.01$ for entire sample and for males; $P = 0.05$ for females). Agricultural use of pesticides ($P = 0.86$) and total deliveries ($P = 0.70$) were not statistically different between cases and controls. Cases and controls did not differ in their reports of blood transfusions ($P = 0.10$). Cases were more likely to have had injection treatments for schistosomiasis ($P < 0.01$).

Combining the cases and controls, we observed the prevalence of antibody to HCV measured by EIA was 42.1% (186/442 total subjects), and the prevalence of current HCV infection as measured by RT-PCR was 33.0% (146/442). Participants who tested positive for anti-HCV antibody but not HCV RNA were presumed to have cleared their HCV infection in the past. These accounted for 40/186, or 21.5% of all those with HCV antibody. Eight participants had evidence of HCV RNA but not antibody, suggesting the possibility either of an acute HCV infection or of a failure to sustain an antibody response to a chronic infection.

Table 2 shows HCV results by case and control status and unadjusted OR by HCV infection status. The first OR column compares cases and controls with evidence of HCV RNA by RT-PCR to those having no HCV RNA. In the entire sample, the OR was 2.3 and was statistically significant (95% CI: 1.5, 3.5).

Table 1 Characteristics of non-Hodgkin's lymphoma (NHL) cases and controls, Egyptian National Cancer Institute, Cairo, Egypt, October 1999–July 2003

	Entire sample		Males		Females	
	NHL Cases N = 227	Controls N = 227	NHL Cases N = 137	Controls N = 137	NHL Cases N = 90	Controls N = 90
Male gender	60.4%	60.4%	NA	NA	NA	NA
Age in 2000: mean years (SD)	48.2 (14.2)	47.7 (13.7)	48.5 (14.3)	47.2 (14.0)	47.8 (14.0)	48.6 (13.4)
Rural place of birth ^a	152 (67.0)	151 (66.5)	90 (65.7)	89 (65.0)	62 (68.9)	62 (68.9)
Rural place of residence	62 (27.3)	89 (39.2)	25 (18.2)	44 (32.1)	37 (41.1)	45 (50.0)
Residence in Upper Egypt	17 (7.5)	40 (17.6)	6 (4.4)	19 (13.9)	11 (12.2)	21 (23.3)
Birth in Upper Egypt	60 (26.4)	78 (34.4)	38 (27.7)	49 (35.8)	22 (24.4)	29 (32.2)
Agricultural pesticide use	50 (22.0)	45 (19.8)	42 (30.7)	39 (28.5)	8 (8.9)	6 (6.7)
Total deliveries, mean (SD)	NA	NA	NA	NA	6.0 (2.9)	5.5 (2.9)
Ever transfused ^b	32 (14.1)	45 (19.9)	18 (13.1)	24 (17.5)	14 (15.6)	21 (23.6)
Injection for schistosomiasis	48 (21.1)	38 (16.7)	41 (29.9)	27 (19.7)	7 (7.7)	11 (12.2)

^a 2 subjects had missing data for place of birth.

^b 1 subject had missing data for transfusion.

Stratifying by gender shows this association was quite similar in females (OR = 2.5) and in males (OR = 2.1). The second OR column in Table 2 incorporates anti-HCV antibody data to stratify the OR by infection status, with the reference group being those who were negative for all HCV markers. These results show that the associations in males and females were limited to those with evidence of current infection with HCV (i.e. HCV RNA positive), and was not present in those with evidence only of previous infection (HCV RNA negative but anti-HCV positive).

Exposures documented to have occurred within the 5 years before NHL diagnosis are unlikely to have contributed to development of NHL. The only possible routes of HCV transmission for which we knew the time of exposure were blood transfusion and anti-schistosomal injections. To assess the possibility that infection with HCV through these exposures in the 5 years prior to the study contributed to the observed HCV-NHL association, OR were recalculated excluding the 34 males and 26 females who reported a transfusion after 1994, and in a separate analysis, excluding those who reported having injections to treat schistosomiasis after 1994 (N = 68 males and

18 females). After the exclusions for recent blood transfusions, among males the HCV-NHL OR adjusted for age was 2.3 (95% CI: 1.3, 4.0) and among females, the OR adjusted for age, place of birth, and total deliveries was 3.5 (95% CI: 1.7, 7.5). After exclusion for anti-schistosomal injections, the HCV-NHL age-adjusted OR for males was 2.2 (95% CI: 1.3, 3.8), and among females the adjusted OR was 3.4 (95% CI: 1.7, 6.8).

Among those cases whose tumour samples were analysed by immuno-histochemistry (N = 58), the crude OR compared with all 227 controls for HCV was 1.7 (95% CI: 0.9, 3.2).

Table 3 shows the per cent change in the age-, gender-, and birthplace- adjusted HCV-NHL OR with the addition of each of the variables that differed significantly between cases and controls in Table 1. For the entire sample and especially for males alone, adjustment for current residence in Upper Egypt resulted in a slight increase in the OR for HCV, in the order of 7% to 17%. For females adjustment for residence in Upper Egypt resulted in only a 3% change in the OR. Adjustment for total number of deliveries (for females) resulted in no fluctuations of the HCV-NHL OR.

Table 2 Crude odds ratios (OR) of anti-hepatitis C virus (anti-HCV) and HCV RNA associated with Non-Hodgkin's Lymphoma, Egyptian National Cancer Institute, Cairo, Egypt, October 1999–January 2003

	Cases ^a N = 220	Controls ^a N = 219	OR	95% CI	OR	95% CI
All						
anti-HCV-/RNA-	114	142	} 1		1	
anti-HCV+/RNA-	12	28		0.9	0.5, 1.6	
anti-HCV+/RNA+	94	52	2.3	1.5, 3.5	2.2	1.4, 3.4
Males						
anti-HCV-/RNA-	71	83	} 1		1	
anti-HCV+/RNA-	10	20		0.8	0.4, 1.6	
anti-HCV+/RNA+	52	32	2.1	1.2, 3.7	2.1	1.2, 3.6
Females						
anti-HCV-/RNA-	43	59	} 1		1	
anti-HCV+/RNA-	2	8		1.2	0.4, 3.3	
anti-HCV+/RNA+	42	20	2.5	1.3, 4.8	2.6	1.3, 5.0

^a 7 cases and 1 control had anti-HCV-/RNA+ viral markers results; 2 controls have missing data for anti-HCV sera testing.

Table 3 Odds ratio (OR), confidence interval (CI), and percentage change (% Δ) in the association of hepatitis C virus (HCV)-RNA positivity with non-Hodgkin's lymphoma (NHL), with adjustment for potential confounders, Egyptian National Cancer Institute, Cairo, Egypt, October 1999–January 2003

	Entire sample			Males			Females		
	OR	95% CI	% Δ	OR	95% CI	% Δ	OR	95% CI	% Δ
Baseline model, adjusted for (gender) and age and rural birthplace	2.7	1.8, 4.1	—	2.3	1.4, 4.0	—	3.4	1.8, 6.6	—
Adjusted for current residence in Upper Egypt	2.9	1.9, 4.5	+7	2.7	1.5, 4.8	+17	3.5	1.8, 6.8	+3
Adjusted for birth in Upper Egypt	2.7	1.8, 4.1	0	2.3	1.4, 4.1	0	3.3	1.7, 6.5	-3
Adjusted for total deliveries	NA	NA	NA	NA	NA	NA	3.4	1.7, 6.8	0

* Δ = percentage change in the HCV odds ratio (compared to the baseline model) after adding and then replacing the specified variable.

NA = not applicable.

Discussion

The association of HCV with NHL has been examined by case series reports and case-control studies in Italy^{10–20} and other countries.^{21–32} Most of the published reports support an association of HCV with NHL, but closer examination suggests caution is due. Some of these studies were based on small sample sizes, had samples that might have been biased in ways that would artificially inflate the association, lacked control groups, and tested for HCV infection by serological rather than nucleic acid tests. Interpretation of these studies is further complicated because information on covariates, while collected in some studies, was not incorporated into the analyses.

The authors of one large, well-designed study concluded that their results did not support an association of HCV with NHL, although the data they report show otherwise. Pioltelli and others³³ matched 300 NHL cases to 600 non-cancer age- and sex-matched controls. Calculations from data reported in that article indicate an HCV-NHL OR of 2.1 (95% CI: 1.4, 3.1), but the authors misreported the CI as (95% CI: 0.7, 27.0) and concluded that they had a non-significant result. On this basis they called for a 're-evaluation' of the HCV-NHL association they had previously reported. In fact, the results of their study are very similar to ours and provide strong support for that association.

The principal finding of the current study is a positive association of current HCV infection with NHL. We found no increased risk of NHL among participants who had cleared infection with HCV or who showed no sign of ever having been infected.

Finding the association only among those currently infected with the virus is consistent with hypotheses about how HCV might increase NHL risk over time, with a minimum latency of several years between HCV infection and NHL development. Conversely, because NHL is a sign of a disordered immune system, it could represent a lower rate of successful viral clearance by NHL patients.

The only possible routes of HCV transmission for which we knew the time of exposure were blood transfusions and anti-schistosomal injections, but when we excluded subjects who reported these exposures prior to 1994 we did not find major changes in the OR for HCV. Other exposures that we did not assess—e.g. injections, surgeries, or tattoos—might have infected participants in the 5 years prior to the study. Still, it is reassuring that removing the influence of such major potential sources of HCV transmission as blood transfusion and anti-schistosomal injection did not affect the estimate of association.

Misclassification of cases and controls may have occurred in this study as diagnoses could not always be independently confirmed due to lack of pathology material. Likewise, immunohistochemical testing to differentiate B-cell from T-cell NHL was done on only a small subset. Immunohistochemistry and histology review were planned as tools with which to establish and confirm diagnoses for all cases, but actually served as quality controls for the diagnoses obtained from the pathology database and medical charts since they could be done in only a few cases.

Some reports have indicated that the relationship of HCV with NHL is confined to particular NHL subtypes, specifically to

lymphoplasmacytoid lymphoma/immunocytoma associated with mixed cryoglobulinaemia type II, or, in the absence of mixed cryoglobulinaemia, with follicular centre, marginal zone, and diffuse large NHL.^{14,34} While immunohistochemical subtyping of NHL was not performed in this study, histopathological classification identified only three lymphoplasmacytic lymphomas in our sample, all of which were negative for HCV RNA. Further immunohistochemistry studies on these materials are in progress in this study population.

The results presented here describe a strong association of chronic HCV infection with the risk of developing NHL, which persisted after adjustment in multivariate models and after several sensitivity analyses. Much remains unknown about the natural history of HCV infection and its possible contribution to carcinogenesis; however, our data suggest that NHL may be among the malignant complications of chronic HCV infection.

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