

High prevalence of hepatitis G virus infection in Hodgkin's disease and B-cell lymphoproliferative disorders: absence of correlation with hepatitis C virus infection

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Background and Objectives. During the last decade an epidemiological association between hepatitis C virus (HCV) and B-cell lymphoproliferative disorders (B-LPD) has been reported; the same association has not been observed for Hodgkin's disease (HD). Hepatitis G virus (HGV) shares genetic and biological features with HCV, thus it might also be involved in lymphomagenesis.

Design and Methods. The aim of this study was to compare the prevalence of HCV and HGV infection in patients at diagnosis of B-LPD or HD.

Results. We tested 227 consecutive untransfused patients (127 with B-LPD and 100 with HD) and 110 healthy controls. The prevalence of HCV infection was significantly higher in B-LPD patients than in controls (17.3% vs. 1.8%, $p < 0.002$), whereas it was the same in HD patients as in controls. In contrast, the prevalence of HGV was significantly higher in patients, both those with B-LPD (7.8% vs. 0.9%, $p < 0.03$) and those with HD (13% vs. 0.9%, $p < 0.002$), than in controls. Among the various B-LPD tested, HGV infection was more frequent in B-NHL (11.5%).

Interpretation and Conclusions. Our data support the hypothesis that HGV infection may play a role in lymphomagenesis and that this role is different and separate from that of HCV.

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Key words: hepatitis C virus, hepatitis G virus, epidemiology, lymphoproliferative disorders, lymphoma, non-Hodgkin's lymphoma, Hodgkin's disease.

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In the last few years, a close association has been established between virus-related chronic hepatitis and mixed cryoglobulinemia.¹ It has also been reported that B-cell lymphoproliferative disorders (B-LPD) are epidemiologically associated with HCV infection, with a prevalence up to 30%.²⁻⁵ In 1995, hepatitis G virus (HGV) was identified, cloned and sequenced.^{6,7} HGV is a new member of the flaviviridae family, sharing considerable structural and biological similarities with HCV. However, HGV shows scarce liver tropism, and its role in chronic liver diseases has not yet been established.^{8,9} The site of HGV replication remains unknown, although *in vitro* and *in vivo* evidence of the presence of HGV in hematopoietic cells has been reported.^{10,11} By analogy with HCV, it has been hypothesized that HGV might be implicated in lymphomagenesis.¹²⁻¹⁴ In this study we investigated the prevalence of HCV and HGV infection in patients suffering from overt lymphoproliferative disorders referred to a single hematologic center in Southern Italy.

Design and Methods

Patients

This study enrolled 227 consecutive patients attending our Institution who suffered from B-cell lymphoproliferative disorders (B-LPD) or Hodgkin's disease (HD). A group of 110 occasional blood donors from the same geographical area was studied as healthy controls. The age and gender ratios were similar in the groups of patients and controls: median age 55 years (range 16-80) and 54 years (25-64), M/F 1.1 and 1.3, respectively. All patients and controls were HIV negative and had never been transfused; no other risk factors for blood-borne diseases were present in patients or controls, except those possibly related to the geographical area. All patients underwent blood tests and lymph node and bone marrow biopsy in order to diagnose and characterize the malignancy.

Detection of antibodies and viral RNA

Patients and controls were tested for anti-HCV antibodies, HCV-RNA and HGV-RNA. The presence of anti-HCV-Ab was assessed by an ELISA 3rd generation test (ORTHO-Diagnostic System, Boston, MA, USA). The presence of HCV-RNA and HGV-RNA in the sera and in circulating lymphocytes was assessed by a polymerase chain reaction (PCR)-based technique. Sera were rapidly (within 30' from blood drawing) frozen at -20° C. RNA was extracted with standard techniques¹⁵ and reverse transcribed using random hexamers. To assess the presence of HCV-RNA, a nested PCR was performed using primers expanding the highly conserved 5' non-coding genomic region.^{16,17} For HGV-RNA, the non-structural genomic region 3 (NS3) and the 5 (NS5) and 5' non-coding regions were amplified.¹⁸ The final PCR products were run on gel-electrophoresis. Carryover contamination was avoided by applying the measures suggested by Kwok and Higuchi.¹⁹ In each experiment positive and negative controls were reverse transcribed, PCR-amplified and analyzed.

The tests were considered positive when results were concordant. RT-PCR was repeated for all positive and indeterminate specimens. The lowest viral concentration detectable was equivalent to 10 copies of viral genome per microliter.¹⁸ For the purpose of this study, we considered as HCV-positive those patients who were positive for both anti-HCV-Ab and HCV-RNA.

Cell separation

Peripheral blood mononuclear cells (PBMNC) were isolated by density gradient centrifugation using a lymphocyte separation medium (Flow Laboratories). After three washings in phosphate-buffered saline (PBS), PBMNC were resuspended in PBS and counted. RNA was extracted from at least 5×10⁶ cells by standard methods (see above).

Statistical analysis

Statistical analysis was performed using Fisher's exact test and the χ^2 test, as suitable. Statistical significance was accepted for any $p < 0.05$.

Results

The prevalence of HCV and HGV infections in the population, as evaluated in the group of healthy controls, was 1.8% and 0.9%, respectively. In the series of 227 unselected and untransfused patients we found that 24 were positive for HCV and 23 were positive for HGV, indicating a prevalence of about 10% for both infections. However, no overlap between the two infections was present: only

Table 1. Prevalence of HCV and HGV infection in lymphoproliferative disorders.

	Tested	HCV+		HGV+	
		n	%	n	%
B-LPD	127	22	17.3	10	7.9
HD	100	2*	2.0	13*	13.0
Total	227	24	10.6	23	10.1
Controls	110	2	1.8	1	0.9

B-LPD, B-cell lymphoproliferative disorders; HD, Hodgkin's disease; *One patient was infected with both HCV and HGV.

Table 2. Prevalence of HCV and HGV in patients with B-cell lymphoproliferative disorders.

	Tested	HCV+		HGV+	
		n	%	n	%
B-NHL	61	12	19.7	7	11.5
MM	48	4	8.3	3	6.3
WM	9	4	44.4	0	
CLL	9	2	22.2	0	

B-NHL, B-cell non-Hodgkin's lymphoma; MM, multiple myeloma; WM, Waldenström's macroglobulinemia; CLL, chronic lymphocytic leukemia.

one patient suffering from HD was found to be positive for both infections.

B-cell lymphoproliferative disorders

Out of 127 patients with a B-LPD, 22 were positive for HCV and 10 were positive for HGV. The prevalence of both infections in B-LPD patients was significantly higher than in the controls: HCV 17.3% vs. 1.8%: $p < 0.002$; HGV 7.8% vs. 0.9%: $p < 0.03$ (Table 1).

The prevalence of HCV infection varied among the different B-LPD (Table 2), ranging from 8% in patients with multiple myeloma (MM) to 44% in patients with Waldenström's macroglobulinemia (WM); in B-cell non-Hodgkin's lymphoma (B-NHL) it was about 20%.

The prevalence of HGV infection was higher in patients with B-NHL (11.5% vs. 0.9%, $p = 0.04$) and in patients with MM (6% vs. 0.9%, $p = 0.08$) than in the controls. Among the few patients with WM or chronic lymphocytic leukemia (CLL), none was found to be infected by HGV.

While we did not note obvious differences between HCV-positive and HCV-negative B-NHL patients, some features of B-NHL were different between HGV+ and HGV- patients (Table 3). The age

Table 3. Clinical and histologic characteristics of 61 patients with B-NHL according to viral status.

n	HGV-/HCV-	HCV+	HGV+
	42	12	7
Gender (female/male)	26/16	10/2	3/4
Age, median (range)	57 (38-76)	57(49-62)	38 (16-77)
Stage: I, II, III, IV	29/2/4/7	2/4/0/6	1/3/0/3
Grade: L/I/H	10/7/25	3/2/7	0/1/6

L, low grade; I, intermediate grade; H, high grade.

Table 4. Clinical and histologic characteristics of 100 patients with Hodgkin's disease according to viral status.

n	HGV-/HCV-	HCV+	HGV+
	86	2*	13*
Gender (female/male)	38/48	1/1	5/8
Age, median (range)	35 (18-70)	35-37	31 (26-42)
Stage: I, II, III, IV	7/62/9/8	0/1/1/0	1/10/1/1
Histology: LP/MC/ NS	1/4/81	0/0/2	0/0/13

LP: lymphocyte predominance; MC: mixed cellularity; NS: nodular sclerosis;
*One patient was infected with both HCV and HGV.

of onset was relatively younger in HGV+ patients (median, 38 years) than in HGV-ones (median, 57 years). Six out of 7 cases of B-NHL in HGV+ patients were high-grade lymphomas: 2 cases of diffuse large B-cell lymphoma, 2 cases of anaplastic large cell lymphoma, one case each of primary mediastinal large B-cell, follicular center cell and lymphocytic lymphoma. Finally, no patient in the HGV+ group had evidence of bone marrow involvement by either histologic or flow cytometric analysis.

Hodgkin's disease

Out of 100 patients with HD, HCV infection was observed in only two, thus the prevalence of this disease was not different from that observed in the control group: 2% vs. 1.8%. By contrast, HGV infection was detected in 13 HD patients; this prevalence is significantly higher than that in the control group (13% vs. 0.9%, $p < 0.002$). Clinical and histologic features of HD in HGV+ and HGV- patients did not differ significantly (Table 4).

Co-infection

In some reports, up to 10% of patients infected by HCV were found to be co-infected with HGV;²⁰ this could raise the possibility that the association of HGV infection with a LPD is mediated by HCV infection. In our series, this hypothesis was ruled out, since only one patient suffering from HD was co-infected, and none in the B-LPD group.

HGV-RNA in peripheral blood mononuclear cells

In order to investigate the hypothesis that lymphocytes are the site of HGV replication, we used PCR to test peripheral blood mononuclear cells from HGV-infected patients for the presence of HGV-RNA. Using a technique that does not separate the positive from the negative strand of viral RNA, we did not detect HGV-RNA in circulating mononuclear cells of any HGV-positive patient.

Discussion

An association between B-LPD and HCV has been recognized during the last decade,²¹ and possible pathogenic mechanisms have been hypothesized.²²⁻²⁴ In addition, it has been suggested that HGV, a flavivirus similar to HCV, may also play a role in lymphomagenesis,¹²⁻¹⁴ but this is still controversial.^{25,26} We tested a group of patients suffering from B-LPD or HD for HCV and HGV at presentation.

In this study we have confirmed previous observations that in Southern Italy the prevalence of HCV infection in patients suffering from B-LPD is higher than that in healthy subjects and that this finding is particularly relevant for patients with B-NHL, CLL and WM.^{3,27} Since the association of HCV with B-LPD has been reported in some geographical areas^{2,4,28-30} but not in others,^{31,32} apparently without obvious correlation with the level of prevalence of HCV infection in the general population in the same areas,^{33,34} it is possible that the oncogenic potential of HCV may become effective only in specific genetic backgrounds and/or in association with some other environmental factors.

In the same group of B-LPD patients, we found a significantly higher prevalence of HGV infection (7.8% vs. 0.9%, $p < 0.03$), in particular in B-NHL patients. The prevalence of HGV infection in B-NHL patients (11.5%) is similar to that found in 69 patients in Germany (13%).³⁵ The size of the sample is too small to subgroup the patients; nevertheless, in our series patients with HGV-associated B-NHL had some distinctive features: younger age of onset, prevalence of high-grade lymphoma (which is in contrast with the predominance of low-grade lymphomas observed in the German series),³⁵ and absence of bone marrow involvement.

When analyzing patients suffering from HD, we found that the prevalence of HCV infection was similar to that in healthy controls, thus confirming that there is no association between HCV infection and HD.^{3,36} In contrast, we found that in the same group of HD patients the prevalence of HGV infection was significantly higher than that in controls (13% vs. 0.9%, $p < 0.002$), an observation nev-

er reported before (with the exception of a preliminary report from our group).¹⁴

As far as it concerns the detection of HGV-RNA in mononuclear cells, the virus has been found in circulating lymphocytes, in bone marrow cells and in lymphoid organs in a proportion of HGV-infected patients,^{11,37,38-43} raising the possibility that lymphoid organs and/or bone marrow are the sites of HGV replication. However, only in a few instances were viral replicative strands detected;^{40,43} thus, despite the documented ability of HGV to replicate in PBMC *in vitro*,¹⁰ the site of replication *in vivo* remains controversial. In our study, using a technique that does not separate the genomic from the replicative viral RNA, we were not able to identify HGV-RNA in circulating mononuclear cells of HGV-infected patients. However, we did not look at viral variants which might have different tropism.⁴⁴

In conclusion, our data in this series of unselected and untransfused patients show that prevalences of both HCV and HGV infections are higher in patients suffering from a lymphoproliferative disease than in healthy subjects, and that this is not due to co-infection. In addition, some features of lymphoproliferative disorders associated with HCV infection seems to be different from those associated with HGV infection; in particular, HGV but not HCV infection is associated with HD. Taken together, these observations support the hypothesis that both HCV and HGV may play a role in lymphomagenesis, and suggest that the pathway they follow to become oncogenic is not identical.

Contributions and Acknowledgments

ADR and MPE were the main investigators, designed the study and were responsible for data collection, and with RN and BR analyzed the data, reviewed the literature and wrote the manuscript. CdG, MPI and LS collected clinical data and were involved in the management of the patients. EP produced the data on the control group and with FdM and GdGR performed the laboratory study. BR and RT took part in the conception and supervision of the study. All the authors were involved in the interpretation of data, and in the drafting and final approval of the manuscript.

Disclosures

Conflict of interest: none.

Redundant publications: <50%; preliminary results on a part of this survey appeared as a Letter to the Editor in *Br J Haematol* 1998; 103:1206-7.

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PEER REVIEW OUTCOMES

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Dr. Peter Karayiannis, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Dr. Karayiannis and the Editors. Manuscript received January 29, 2002; accepted May 6, 2002.

What is already known on this topic

HGV has been detected by PCR in peripheral blood mononuclear cells, but whether the virus replicates productively in these cells still remains unclear. As HGV infection has not been linked with any well defined disease entity, it is important to know whether it is linked with any of the lymphoproliferative disorders.

What this study adds

This study looked at 227 patients with such disorders and both serum HCV- and HGV-RNA were detected at a significantly higher rate in patients with B-LPD than in controls, whilst in the HD group this was the case for HGV-RNA alone. Thus, there was an association of HGV infection with both disease groups.

Potential implications for clinical practice

The findings of this study have no bearing on the management of patients with such disorders. Further studies are needed to establish a clear etiological association between these disorders and HGV infection, and in particular, obtain evidence of replication of the virus in lymphoid cells, which was lacking in the present study.

Peter Karayiannis, Associate Editor