Hepatitis C virus infection and acute or chronic glomerulonephritis: an epidemiological and clinical appraisal

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Abstract

Background. The relationship between hepatitis C virus (HCV) infection and acute or chronic glomerulonephritis (GN) is not well understood.

Methods. Two hundred and eighty-four patients with biopsy-proven GN and other renal diseases were studied in a multicentre survey performed during the period 1992–1995. Several clinical parameters were collected for each patient at the time of renal biopsy. We made a multivariate analysis by logistic regression model to evaluate the independent association of clinical and histological patient characteristics with HCV infection, as detected by anti-HCV antibody testing.

Results. The prevalence of anti-HCV positivity was 13% (38/284). The frequency of anti-HCV positivity ranged between 0 and 100% in the different types of renal diseases, the difference was statistically significant (P=0.0001). The anti-HCV rate was significantly higher in patients with cryoglobulinaemic membranoproliferative and mesangioproliferative GN than among the other individuals (14/14 (100%) vs 24/270 (9%), P=0.0002). Our multivariate analysis by logistic regression model showed that age (P=0.0017) and type of renal diseases (P=0.0007) were independently and significantly associated with anti-HCV antibody.

Conclusions. We observed strong association between HCV infection and cryoglobulinaemic GN. Age and type of renal disease were important independent predictors of anti-HCV positivity in our cohort of patients. Three anti-HCV-positive patients with membranous nephropathy did not show significant remission of nephrotic proteinuria after treatment with interferon-alpha. Our data do not appear to support an association between HCV and non-cryoglobulinaemic GN. Further epidemiological surveys, experimental studies and clinical trials are warranted to fully elucidate the role of HCV in non-cryoglobulinaemic GN.

Key words: HCV; cryoglobulinaemic and non-cryoglobulinaemic glomerulonephritis; interferon therapy

Introduction

The hepatitis C virus (HCV) is an RNA virus recognized as the major cause of transfusion-associated [1] and 'community-acquired' [2] non-A, non-B hepatitis. Patients with chronic HCV infection are at risk to develop chronic active hepatitis, cirrhosis, and hepatocellular carcinoma [3]. Moreover, numerous extrahepatic manifestations of HCV infection have been previously reported including porphyria cutanea tarda [4,5], Hashimoto’s disease [6,7] and lymphocytic sialadenitis [8,9]. In addition, several epidemiological investigations [10–14], case reports [15–23], clinical trials [24] and experimental results [25] have emphasized the association between HCV infection, essential mixed cryoglobulinaemia, and its principal renal lesion, cryoglobulinaemic membranoproliferative GN.

In contrast, data from investigations into the relationship between HCV infection and non-cryoglobulinaemic membranoproliferative GN, membranous nephropathy, or other glomerular diseases are scarce and with conflicting results. Recently, some serological investigations from Europe [26–29] and Asia [30,31] showed a very low anti-HCV prevalence in adult patients with primary glomerular diseases. A survey [32] performed among paediatric patients with 'idiopathic' membranoproliferative glomerulonephritis in the US was unable to detect HCV in any of the subjects. On the contrary, several authors have treated
with interferon-alpha numerous anti-HCV-positive individuals with non-cryoglobulinaemic membranoproliferative GN [33], membranous nephropathy [34], focal sclerosing [33], or fibrillary glomerulonephritis [35]; they observed improvement of renal function after completion of interferon therapy, this trend coinciding with suppression of HCV viraemia. Moreover, many anecdotal cases [36–41] of HCV-infected patients showing various non-cryoglobulinaemic glomerular diseases have been observed. Recent experimental investigations [42] were able to detect HCV in the renal tissue of patients with HCV infection and membranous glomerulonephritis. Such conflicting results prompted the present investigation.

The aim of this multicentre study was to evaluate the prevalence of HCV infection, as assessed by anti-HCV antibody testing, and its relationship with clinical or morphological features in a large cohort of patients with biopsy-proven glomerulonephritis and other renal diseases. In addition, we treated three patients presenting HCV-related liver disease, membranous nephropathy, and nephrotic proteinuria with interferon-alpha as a therapy for the liver and kidney diseases.

Subjects and methods

Study design

We collected the clinical and histological features of the patients who consecutively underwent renal biopsy at four Nephrology Units of Northern and Central Italy during the period 1992–1995. The following information in all patients at the same time as the renal biopsy was reported: gender, age, proteinuria (normal range <0.15 g/24 h), serum creatinine (normal range 53–115 μmol/l), detectable serum cryoglobulins, patient allocation among centres, HBsAg status, and histology of renal disease. There were 41 (14%) patients from Unit 1, 108 (38%) from Unit 2, 51 (18%) from Unit 3, and 84 (30%) from Unit 4. Among the patients (n=108) referred to the Unit 2 (Nephrology and Dialysis Division of Lecco Hospital) we identified three patients with HCV-related liver damage, membranous nephropathy, and proteinuria in the nephrotic range. They were treated with 3 million units of lymphoblastoid interferon-alpha (Wellferon, Wellcome) given subcutaneously three times per week for time periods as reported below.

Study group

There were 181 males and 103 females, the mean age of the patients was 51.2±23 years, the median value of proteinuria was 2.5 g/24 h (range 0–21.9), the median level of serum creatinine was 111 μmol/l (range 44–108).

In our study group we have identified a subgroup (n=205) of cases of primary GN: IgA nephropathy (n=61), minimal-change disease (n=24), focal sclerosing GN (n=39), membranoproliferative GN (n=10), membranous nephropathy (n=55), diffuse mesangio proliferative GN (n=13), and crescentic GN (n=3). There was a second subset (n=79) of patients with secondary GN and other renal diseases, as follows: diabetic glomerulosclerosis (n=4), cryoglobulinaemic GN (n=14), lupus nephritis (n=12), Henoch–Schönlein syndrome (n=1); myeloma kidney (n=2), amyloidosis (n=11), aspecific sclerotic lesions (n=4), Goodpasture’s syndrome (n=2), post-infectious GN (n=5), hereditary GN (n=1), HIV-associated GN (n=2), polyarteritis nodosa (n=2), Churg–Strauss syndrome (n=1), Wegener’s granulomatosis (n=1), microscopic polyarteritis (n=10), interstitial nephritis (n=4). In the subgroup of patients with cryoglobulinaemic GN there were subjects with membranoproliferative (n=12) and mesangio proliferative (n=2) GN.

Serological methods

Epidemiology of HCV infection was assessed by testing for anti-HCV antibodies. Antibodies to HCV were measured by a second-generation recombinant immunoblot assay (RIBA TM HCV 2.0 Strip Immunoblot Assay (SIA); Abbott Laboratories, North Chicago, IL), based on the reverse-hybridization principle [45]. HCV genotypes were classified using the nomenclature of Simmonds et al. [46].

Virological assays

In anti-HCV-positive samples the presence of HCV RNA was detected by reverse-transcription polymerase chain reaction (RT-PCR). We used Amplipcr HCV test (Roche Diagnostic Systems, Nutley, NJ), as previously reported by others [44], using primer sets from the 5’ untranslated region of the HCV genome. The HCV genotypes in the serum samples of anti-HCV positive samples were detected by a hybridization assay, called line probe assay (LiPA, Innogenetics, Zwijndrecht, Belgium), based on the reverse-hybridization principle [45]. HCV genotypes were classified using the nomenclature of Simmonds et al. [46].

Renal histology

Renal tissue was obtained by percutaneous renal biopsy in all patients. The kidney-biopsy specimen obtained from each patient was divided into three parts for light microscopy, direct immunofluorescence, and electron microscopic studies. These analyses were made with standard procedures.

Statistical analysis

Data are expressed as mean±standard deviation. Non-parametric data are expressed as median with respective ranges. Group comparisons were made by Student’s t test for parametric data and Mann–Whitney test for non-parametric data. Chi-square test with Bonferroni’s correction was used for comparison of anti-HCV prevalence in the different patient groups. A multivariate analysis with nominal logistic technique was conducted. A nominal regression by maximum likelihood for a single nominal response was performed. In our model anti-HCV positivity was included as the dependent variable; gender, age, proteinuria, serum creatinine, HBsAg status, patient allocation among centres, and type of renal disease were predictor variables. Two categories of renal disease were included in the model:
primary GN (n = 205) and secondary GN or other nephropathies (n = 79). A P value of less than 0.05 was used to indicate statistical significance. Statistical analysis was performed using the statistical package JMP IN, Macintosh format, version 3.1.7, ©SAS Institute Inc, USA.

Results

Epidemiological survey

Univariate analysis. The prevalence of HBsAg positivity was 3% (9/284). The prevalence of anti-HCV antibody was 13% (38/284) in the whole population. There were 38 (13%) of 284 patients positive by ELISA HCV 2.0 and confirmed by RIBA TM HCV 2.0 SIA. Twenty-nine (76%) of 38 were positive by RIBA TM HCV 2.0 SIA, and 9 (24%) of 38 gave ‘indeterminate’ reactivity by RIBA TM HCV 2.0 SIA. Twenty-eight (74%) of 38 were tested by RT-PCR, 21 (75%) of 28 were positive by RT-PCR and seven (25%) of 28 tested negative by RT-PCR. The results obtained by RT-PCR are shown in Table 1. The analysis by HCV genotyping showed 12 (57%) patients with HCV genotype 1b, one (5%) patient with HCV genotype 1a, three patients (14%) with HCV genotype 2a–2c, three (14%) patients with HCV genotype 2a. Two (10%) patients positive by RT-PCR had low viraemic levels and were unable to be typed. There was no significant association between HCV genotyping and renal histology.

The anti-HCV positivity was 9% (19/205) in the subset of patients with primary GN, and 24% (19/79) in the subgroup of subjects with secondary GN and other renal diseases, the difference was statistically significant (P = 0.002).

Table 1 reports the prevalence of HCV infection, as detected by anti-HCV testing, in the most important types of GN of our series. As shown, the prevalence of anti-HCV positivity in various types of GN ranged between 0% and 100%; the anti-HCV rate changed significantly (P = 0.0001). The frequency of anti-HCV positivity in the patients with cryoglobulinaemic GN was significantly higher than among the other individuals (14/14 (100%) vs 24/270 (9%), P = 0.0002). The frequency of anti-HCV positivity among patients with cryoglobulinaemic GN, non-cryoglobulinaemic membranoproliferative GN, and membranous nephropathy was significantly higher than in the other patients, 26/79 (33%) vs 12/205 (6%), P = 0.0002.

The clinical features of anti-HCV-positive and anti-HCV-negative patients are reported in Table 2. As shown in Table 2, only age was significantly higher in anti-HCV-positive than in anti-HCV-negative individuals.

Table 2. Clinical features of anti-HCV-positive and -negative patients

<table>
<thead>
<tr>
<th>Anti-HCV pos</th>
<th>Anti-HCV neg</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>38</td>
<td>246</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>25/13</td>
<td>157/89</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.8 ± 12</td>
<td>48.7 ± 17</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>3.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>133</td>
<td>106</td>
</tr>
<tr>
<td>HBsAg pos.</td>
<td>1 (3%)</td>
<td>8 (3%)</td>
</tr>
</tbody>
</table>

Multivariate analysis

Application of a logistic regression model to our group showed that age (P = 0.0017) and type of renal disease (P = 0.0007) were independent predictors of anti-HCV positivity (Table 3). The other parameters included in the model did not show significant and independent association with anti-HCV antibody.

Table 3. Multivariate analysis with logistic regression

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>STD error</th>
<th>Chi-square</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>0.1584</td>
<td>0.2079</td>
<td>0.58 0.4461</td>
</tr>
<tr>
<td>Age</td>
<td>−0.0431</td>
<td>0.0137</td>
<td>9.90 0.0017</td>
</tr>
<tr>
<td>Type of renal disease</td>
<td>0.7064</td>
<td>0.2079</td>
<td>11.54 0.0007</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>−0.0052</td>
<td>0.0496</td>
<td>0.01 0.9150</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.1981</td>
<td>0.1311</td>
<td>2.28 0.1309</td>
</tr>
<tr>
<td>HBsAg</td>
<td>0.1638</td>
<td>0.4153</td>
<td>0.16 0.6932</td>
</tr>
<tr>
<td>Unit 1</td>
<td>−0.1477</td>
<td>0.3210</td>
<td>0.21 0.6454</td>
</tr>
<tr>
<td>Unit 2</td>
<td>−0.8238</td>
<td>0.3910</td>
<td>4.44 0.0352</td>
</tr>
<tr>
<td>Unit 3</td>
<td>−0.3358</td>
<td>0.3331</td>
<td>1.02 0.3134</td>
</tr>
</tbody>
</table>

Table 1. Positivity for anti-HCV antibody and HCV RNA in various types of glomerulonephritis

<table>
<thead>
<tr>
<th>Anti-HCV positivity</th>
<th>HCV RNA positivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA nephropathy</td>
<td>4/61 (6%)</td>
</tr>
<tr>
<td>Minimal-change nephrosis</td>
<td>1/24 (4%)</td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>0/12 (0%)</td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>10/35 (18%)</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis</td>
<td>2/10 (20%)</td>
</tr>
<tr>
<td>Focal sclerosing glomerulonephritis</td>
<td>2/39 (5%)</td>
</tr>
<tr>
<td>Mesangio proliferative glomerulonephritis</td>
<td>0/13 (0%)</td>
</tr>
<tr>
<td>Post-infectious glomerulonephritis</td>
<td>1/3 (12%)</td>
</tr>
<tr>
<td>Cryoglobulinaemic glomerulonephritis</td>
<td>14/14 (100%)</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>1/15 (7%)</td>
</tr>
<tr>
<td>Others</td>
<td>3/33 (9%)</td>
</tr>
</tbody>
</table>
Case reports

Patient 1

Patient 1 is a 62-year-old white male with a history of type-II diabetes, depression, and alcohol abuse. Past medical history was also significant for persistently elevated liver enzymes for several years. He underwent liver biopsy in 1981 (active chronic hepatitis), and in 1982 (post-hepatitis cirrhosis). He denied a history of lupus, non-steroidal anti-inflammatory drug use, kidney disease, and transfusions. He presented to the Nephrology Division of Lecco Hospital in 1989. His creatinine clearance (normal range 1.5–2.2 ml/s) was 1.45 ml/s with serum creatinine of 117 μmol/l and 10.3 g of urinary protein/24 h. A renal biopsy revealed membranous nephropathy (stage II). He received pulsed corticosteroid therapy with no improvement of renal function or proteinuria.

He was followed up in the outpatient clinic at Lecco Hospital until July of 1994 when he was admitted again to the Nephrology Division. Laboratory examination (July 1994) showed: serum creatinine 102 μmol/l, creatinine clearance 1.74 ml/s, proteinuria 10.8 g/24 h, a serum albumin (normal range 38–45 g/l) of 28 g/l. AST (normal range < 0.67 μkat/l) and ALT (normal range < 0.75 μkat/l) values were 2.1 μkat/l and 3 μkat/l respectively. He was found to be HCV antibody positive (anti-HCV ELISA-2 positive; RIBA™ HCV 2.0 Strip Immunoblot Assay (SIA) positive), HBsAg negative, anti-HBc negative, anti-HBs positive, and HIV negative. Prothrombin time (PT) and complement studies (C3, C4) were normal, rheumatoid factor (RF) and cryoglobulins negative. His physical examination was remarkable for hepatomegaly, lower-extremity oedema, and ascites.

The patient was placed on 3 million units of interferon-alpha three times per week (7.94). At initiation of treatment, his creatinine was 99.9 μmol/l with 10.8 g urinary protein/24 h, and a creatinine clearance of 1.73 ml/s. AST and ALT levels were 1.7 and 1.8 μkat/l respectively; he tested positive by RT-PCR and showed genotype HCV 1b. After 5 months interferon-alpha was stopped because of fatigue, nausea, and headache; the patient’s urinary protein excretion was 7.2 g protein/24 h, liver enzymes were normal (AST 0.45 μkat/l and ALT 0.32 μkat/l), creatinine remained at 97.2 μmol/l, creatinine clearance was 1.65 ml/s. He was viraemic by RT-PCR. After discontinuing alpha-interferon, serum aminotransferase levels remained stable for 1 year.

Patient 2

Patient 2 is a 50-year-old white male with a history of myocardial infarction and porphyria cutanea tarda. The patient denied a history of lupus, diabetes, non-steroidal anti-inflammatory drug use, kidney disease, or blood transfusions. He had had raised aminotransferase levels since 1993; he then suspended alcohol use. The patient was referred to the Nephrology Division of Lecco Hospital in December 1994 with proteinuria 7.5 g/24 h. The physical examination was remarkable for lower-extremity oedema. Laboratory data revealed the following: serum creatinine 67.2 μmol/l, creatinine clearance 1.67 ml/s, albumin 22 g/l, AST 1.1 μkat/l, ALT 1.1 μkat/l, C3 (normal values 0.56–1.05 g/l) 1.04 g/l, C4 (normal values 0.15–0.43 g/l) 0.19 g/l, cryoglobulins and ANA negative. Second-generation anti-HCV antibody (ELISA and RIBA™ SIA) was positive, HBsAg, anti-HBc, and HIV were negative. Anti-HBs was positive. He showed HCV RNA by RT-PCR and HCV genotype 1b. The renal biopsy (December 1994) revealed membranous GN (stage I–II). A liver biopsy (December 1994) showed chronic active hepatitis with mild fibrosis.

The patient was started on 3 million units of interferon-alpha three times weekly and treated for 6 months. At the end of the treatment period his urinary protein excretion was 7.6 g/24 h, the creatinine was 68.9 μmol/l, creatinine clearance 1.82 ml/s, serum albumin was 17.4 g/l. AST 0.37 and ALT 0.52 μkat/l, he was negative by RT-PCR technique. Serum creatinine and urinary protein remained stable 1 year after completion of interferon-alpha therapy; hepatic enzymes rose slightly, with AST and ALT of 0.68 and 0.96 μkat/l respectively.

Patient 3

Patient 3 is a 61-year-old white male who presented to the Nephrology Division of Lecco Hospital in March of 1994 with pitting oedema and nephrotic-range proteinuria. He denied a history of lupus, diabetes, non-steroidal anti-inflammatory drug use, kidney disease, hepatitis or blood transfusions. His hypertension was well controlled with low-dose loop diuretics prior to and throughout alpha-interferon therapy. Laboratory studies were significant for the following: proteinuria 9.7 g/24 h, serum creatinine 57.5 μmol/l, creatinine clearance 2.09 ml/s. Antinuclear antibody (ANA) and cryoglobulins negative, rheumatoid factor (RF) negative, C3 and C4 0.8 and 0.26 g/l respectively. AST 1.2 and ALT 2.7 μkat/l, albumin 24 g/l. HCV antibody positive (second-generation ELISA and RIBA™ SIA), HBsAg negative, HIV negative. He showed HCV RNA by RT-PCR and had HCV genotype 1b. A renal biopsy was performed in March of 1994 which revealed membranous nephropathy (stage II–III). A liver biopsy at the same time as the renal biopsy was consistent with chronic active hepatitis showing mild piecemeal necrosis.

The patient was started on 3 million units of interferon-alpha thrice weekly. At the end of the treatment with interferon-alpha, proteinuria was 9.5 g/24 h and serum creatinine was 53.9 μmol/l, creatinine clearance 1.83 ml/s. Liver enzymes remained elevated (AST 0.83 and ALT 1.65 μkat/l). He tested positive by RT-PCR.
Discussion

Although it is well known that hepatitis B virus may cause GN [47], mainly membranous and membrano-proliferative GN, HCV-related GN has been only recently reported. In addition to cryoglobulinemic membranoproliferative GN [10–25] and IgA nephropathy [48], HCV infection has been described in association with ‘idiopathic’ membranoproliferative GN [13,33], membranous nephropathy [33–34,36–40] mes- angioproliferative GN [41], focal sclerosing [33], and fibrillary GN [35]. Moreover, several cases of de novo hepatitis C-associated GN have been recently reported in HCV-infected patients after bone marrow [38], liver [16,49], and kidney [50–53] transplantation, only some of them showing cryoglobulinaemia or rheumatoid factor.

In our multicentre study we showed a very strong association (100% rate) between cryoglobulinemic GN and HCV, as detected by anti-HCV testing. Moreover, we found a high prevalence of anti-HCV in patients with non-cryoglobulinemic membrano- proliferative GN and membranous nephropathy (20 and 18% respectively). Even when corrected for age, the prevalence of HCV infection in comparable general population of the Milan area [54] is only about 7%.

In accordance with such data and the recent evidence accumulated in the literature [33–35], we treated three anti-HCV-positive patients presenting HCV-related liver disease, membranous nephropathy, and nephrotic proteinuria with interferon-alpha in standard doses. In contrast with the results obtained by Arabian [33] and American [34,35] investigators, patients of our series did not show improvement of renal function after therapy with interferon-alpha. Furthermore, two patients had lowering of hepatic enzyme levels into the normal range at the end of the treatment, this is probably related to the interferon-alpha activity. Thus, in these two patients the unchanged levels of proteinuria at the end of the therapy are not probably related to a poor responsiveness of HCV genotype to interferon.

Such lines of evidence do not appear to support an aetiological role of HCV in the development of membranous nephropathy in our population. Other therapeutic options in these individuals include a second course of interferon-alpha perhaps in a higher dosage or for a prolonged period. A sustained clinical remis- sion following therapy with high-dose interferon-alpha has been recently observed in one patient with HCV-associated cryoglobulinaemic membranoproliferative GN [55]. This may not be an option in some patients because of intolerable side-effects. Alternatively, the use of a second antiviral agent to potentiate or add to the activity of interferon-alpha or the adoption of a different type of interferon would be promising. On the other hand, an improvement in renal function after treatment with interferon has been reported in some but not all patients with HBV-associated membranous nephropathy [56].

The high anti-HCV prevalence we observed in patients with membranous nephropathy and non-cryoglobulinemic membranoproliferative GN is rather difficult to evaluate as these patient subgroups were not very large (n = 55 and 10 respectively); but it might be interesting in the light of the recent evidence [13,33–40] indicating that HCV may be a major cause of non-cryoglobulinemic GN. In contrast, our multi- variate analysis emphasized the importance of age as independent predictor of anti-HCV antibody in our population. Also in the general population the anti- HCV prevalence increases [54] with age, as did HBV markers. In addition, the type of renal disease was significantly and independently associated with anti- HCV in our multivariate analysis; this is probably related to the very high rate (100%) of anti-HCV among patients with cryoglobulinemic GN.

Our epidemiological investigation and clinical trial appear to confirm the hypothesis that the association between non-cryoglobulinemic GN and HCV does not exist in Europe. In contrast, the experience accumulated in USA [13,34,35] and Saudi Arabia [33], implies a role of HCV in non-cryoglobulinemic GN. Likewise HCV-associated GN, HBV-associated GN has been frequently reported in some geographical areas, such as Poland [57], Korea [58], Japan [59], and Africa [60], but it is rare in the United States [61,62] and Western Europe [47]. We are planning to study the predictors of anti-HCV positivity in larger cohorts of subjects with biopsy-proven glomerular diseases.

One possibility is that in some cases of hepatitis-C- associated GN who have neither tissue nor serological evidence of cryoglobulins, the production of cryoglobulins might not reach a level that would be easily detected by standard laboratory techniques. Also, some patients with HCV-associated GN might produce antibody with the biological features of ‘rheumatoid factor’ but without the ability to induce immune complex precipitable in the cold. Alternatively, these individuals could develop an immunocomplex GN with no detectable circulating cryoglobulins. In our survey, testing for cryoglobulins in serum was performed at the time of renal biopsy in all patients; a longitudinal observa- tion over the ensuing months could detect circulating cryoglobulins in additional individuals, as has previously occurred [24]. However, it might be possible that we are not simply missing the cryoglobulins in the serum of some patients with HCV-associated GN. Indeed, it has been postulated [63] that only anti- HCV-positive patients who produce non-neutralizing antibodies develop some form of glomerulopathy, and the different patterns of glomerular injury observed so far may be related to the appropriateness of the immune response to HCV. The precise mechanisms responsible for a virus-induced nephropathy in humans have been only partially elucidated to date [47], and these suggestions remain speculative.

In patients with IgA nephropathy, focal sclerosing and proliferative mesangial GN, and minimal-change disease, the prevalence of HCV infection was low, ranging between 0 and 6%. This result is in agreement
with the epidemiological investigations made in Europe so far [26,28]. The anti-HCV prevalence was null in our patients with lupus nephritis, in contrast with previous observations [64]. In the subset of patients with post-infectious GN the anti-HCV prevalence was 12%, but the size of this group \( n=8 \) was very small.

In conclusion, this current multicentre survey confirmed the strong relationship between cryoglobulinaemia GN, and anti-HCV. Our epidemiological investigation and clinical trial do not appear to support an association between HCV and non-cryoglobulinaemic GN. Further epidemiological studies, experimental data, and clinical trials are needed to clarify the role of HCV in non-cryoglobulinaemic GN definitively.

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References


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