Chronic Urticaria Is Not Significantly Associated With Hepatitis C or Hepatitis G Infection

A Case-Control Study

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Objective: To study the prevalence of hepatitis C virus (HCV) and hepatitis G virus (HGV) infection in patients with chronic urticaria.

Design: Prospective case-control study and literature review.

Setting: Dermatology department of an academic medical center in Strasbourg, France.

Patients: One hundred ten consecutive patients with typical urticaria lasting longer than 2 months were seen between March 1, 1997, and August 31, 1998. None had a history of viral hepatitis. Age- and sex-matched patients (n = 110) seen in the same department and during the same period were included for controls. None of the controls had a history of urticaria, pruritic dermatosis, or hepatitis.

Main Outcome Measures: The detection of HCV antibodies through a third-generation enzyme-linked immunosorbent assay. To detect early HCV infection without plasmatic antibodies, genomic amplification of HCV RNA was carried out in all patients using 2 different methods. Hepatitis G virus RNA was detected only by genomic amplification. All measures were planned before data collection.

Results: Antibodies to HCV were found in 1 patient with urticaria and in 1 of the control group (0.9% of each group). None had circulating HCV RNA, and liver function test results were within the reference range. Genomic amplification without HCV antibodies was not observed. Two patients with urticaria and 2 of the control group (1.8% of each group) had circulating HGV RNA, but they had neither coinfection with HCV nor changes in their liver function test results.

Conclusions: Systematic HCV screening in patients with chronic urticaria is not cost-effective, at least in Europe, because hepatitis C rates were similar to those of the general population. We could not confirm the hypothesis that urticaria occurs in an early phase of HCV infection—ie, before evidence of HCV can be detected by serologic testing. Hepatitis C virus is unlikely to be the cause of urticaria in the infected patient detected in this study because of the absence of HCV RNA and changes on liver function tests. Hepatitis G virus is also unlikely to be a cause of urticaria, as the rate of HGV positivity in this study was even lower than that in the general French population.

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HEPATITIS C virus (HCV) was discovered in 1989,1 and since the development of serologic tests, many authors have investigated associations between HCV infection and cutaneous diseases. In 1995, Pawlotsky et al2 reviewed all published associations and showed that a variety of diseases can be linked with HCV infection. Nevertheless, no physiopathologic data have demonstrated how HCV can induce or trigger skin conditions. In at least 2 cutaneous diseases—mixed cryoglobulinemia3 and porphyria cutanea tarda4—HCV plays an important role. The link between HCV and lichen planus is likely to be important, although this point remains controversial.5-6 Pruritus can be a major symptom in HCV-infected patients7,8 independent of specific cutaneous findings. In some patients, pruritus can be caused by urticaria.7 Urticaria is classically8,10 considered to be a symptom of hepatitis A and hepatitis B infections. Therefore, a possible association of urticaria with HCV infection should not be surprising.

For editorial comment see page 1401

The association of HCV infection with acute urticaria was described11 during the early years of the investigation of HCV, although similar observations were rarely published by other authors. A link between
PATIENTS AND METHODS

PATIENTS

All patients seen from March 1, 1997, to August 31, 1998, in the dermatology department of the University Hospital, Strasbourg, France, with urticaria lasting at least 2 months were included in this study. Patients with known hepatitis or human immunodeficiency virus infection were not included, although we did not see any case of urticaria in patients observed for chronic HCV infection during this period. Patients with fixed or purpuric urticaria suggestive of urticarial vasculitis were not included. One hundred ten consecutive patients with typical urticaria of at least 2 months' duration were included. Forty-three were men and 67 were women; their mean age was 42.1 years (age range, 19-80 years). The median duration of urticaria was 9 months (range, 2-120 months). Associated symptoms were involvement of the lips (n = 12), edema of the tongue (n = 6), dyspnea (n = 6), nausea (n = 1), arthralgia (n = 5), and hypotension (n = 2). All other patients had typical cutaneous lesions of urticaria without mucosal or systemic involvement.

The patients were compared with 110 age- and sex-matched control subjects included during the same period and from the same institutional setting. None of these control patients had urticaria, chronic pruritus, pruritic dermatologic conditions, or known HCV infection. Forty-three were men and 67 were women; their mean age was 43.7 years (age range, 18-85 years). Most of the control patients (n = 38) were being observed for cutaneous malignancies (mainly melanomas), and the rest comprised patients with various conditions—bacterial infections, autoimmune diseases, diabetes mellitus, leg ulcers, allergicologic testing, and benign tumors.

VIROLOGICAL INVESTIGATIONS

To rule out false-negative test results due to late seroconversion, we tested for HCV antibodies and HCV RNA. The HCV antibodies were detected in serum specimens using a commercial third-generation ELISA (Abbott Laboratories, South Pasadena, Calif). The results were interpreted according to the manufacturer's instructions. Hepatitis C virus RNA was detected using 2 methods of reverse transcription, followed by genomic amplification (RT-PCR). The first RT-PCR method had been developed in the Virology Laboratory of Strasbourg13 and is extremely sensitive. Using serial dilutions, the cutoff of this method proved to be as low as 5 Eq of genome per microliter. Briefly, after total RNA extraction from plasma, the pellets were resuspended in water treated with diethylpyrocarbonate. A first RT-PCR round was performed using primers from the conserved sequences of the 5' untranslated region of the HCV genome. The amplified products were submitted to a second RT-PCR round using a pair of internal primers. The amplified product of this nested PCR method was visualized by 2% agarose gel electrophoresis and ethidium bromide staining. The second PCR product was 126 base pairs.

Because false-positive results are likely to occur with a sensitive RT-PCR, all RT-PCR tests were done in duplicate. In patients with positive (2 consecutive positive RT-PCR) and discrepant results (1 positive and 1 negative RT-PCR), a commercial RT-PCR test (AmpliCor HCV; Hoffmann-LaRoche Inc, Basel, Switzerland) was carried out according to the manufacturer's instructions to confirm the result. This test is less sensitive (detection limit: 1000 copies per microliter), but it is standardized.

Because no serologic test is available, HGV RNA was detected by an RT-PCR method, performed in duplicate, as previously described.17 The RT-PCR was performed after total plasmatic RNA extraction, using primers derived from the 470-20-1 sequence of the HGV genome (primer 77F: 5'-CTCTTTGTGGTAGAGCCGAGAGAT-3' and primer 211R: 5'-TCGGTTACTGAGAGCAGCTCAGATGAG-3'). Amplification, the specific products were detected with a probe labeled with phosphorus 32 (152F: 5'-TGCGTTACTGAGCAGCTCAGATGAG-3').

OTHER INVESTIGATIONS

In all patients with urticaria, the following laboratory investigations were also done: aminotransferase, alkaline phosphatase, γ-glutamyltransferase, and bilirubin levels; antinuclear antibodies, rheumatoid factor, and cryoglobulinemia; and antibodies to Helicobacter pylori (threshold value, 10 U/mL)24 and Toxocara canis.25 Physical urticaria was also investigated by a pressure test, a search for urticarial dermographism, and the ice cube test.
with oral lichen planus. The prevalence and possible role of HGV in urticaria have not, to the best of our knowledge, been previously studied.

To analyze the prevalence of HCV and HGV infection in patients with chronic urticaria, we performed a prospective case-control study using both serologic and molecular methods.

RESULTS

The results of virological investigations are detailed in Table 1.

**HCV TESTS**

Among the 110 patients with urticaria, only 1 (0.9%) had HCV antibodies (95% confidence interval, 0%-2.9%), but no HCV RNA could be detected by the 2 RT-PCR methods. Liver function test results in the 1 HCV-positive patient were within the reference range. In the control group, 1 (0.9%) of the 110 patients was HCV positive (95% confidence interval, 0%-2.9%) but had no detectable circulating HCV RNA. There was no difference in the HCV prevalence between patients with urticaria and controls. We did not find HCV RNA in any of the patients that could indicate HCV infection in an early phase, despite the absence of HCV antibodies.

Discrepant results between the first 2 RT-PCRs were found in 9 patients with urticaria and 4 patients in the control group. None of these patients had circulating HCV antibodies, and RT-PCR results in controls using a commercial genomic amplification technique (done in duplicate) were normal. The initial RT-PCR results were, therefore, considered false positive. These patients had no risk factors for HCV, and none had abnormal results on their liver function tests.

The unique patient in the urticaria group with HCV antibodies detected by ELISA had no detectable circulating HCV RNA. He did not have any risk factor for HCV infection—blood transfusion, intravenous drug use, or tattoos. At the time of this study, all his liver function test results were normal and remained so after 3 months of follow-up. No other cause of urticaria could be demonstrated in this patient. In the control group, 1 patient showed HCV antibodies. This patient had received a blood transfusion 10 years ago. At the time of this study, the patient had no circulating HCV RNA, and his liver function test results were within the reference range. No liver biopsy was performed because of repeatedly normal results on liver function tests in these 2 patients.

**HGV TESTS**

Two patients in the urticaria group had HGV RNA, as did 2 control patients (1.8%; 95% confidence interval, 0%-3.5%, for both groups). Therefore, the prevalence of HGV infection did not differ between the 2 groups. No discrepant results were found between duplicate RT-PCRs. Liver function test results in these 4 HGV-positive patients were within the reference range. None of the patients were coinfected with HCV.

### Table 1. Virological Results in 110 Patients With Urticaria and 110 Controls*

<table>
<thead>
<tr>
<th>Results</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urticaria Group</td>
</tr>
<tr>
<td>Hepatitis C virus (HCV)</td>
<td></td>
</tr>
<tr>
<td>ELISA (+), RT-PCR (+)</td>
<td>0</td>
</tr>
<tr>
<td>ELISA (+), RT-PCR (−)</td>
<td>1</td>
</tr>
<tr>
<td>ELISA (−), RT-PCR (−)</td>
<td>100</td>
</tr>
<tr>
<td>ELISA (−), RT-PCR (+/−)†</td>
<td>9</td>
</tr>
<tr>
<td>Hepatitis G virus (HGV)</td>
<td></td>
</tr>
<tr>
<td>RT-PCR (+)</td>
<td>2</td>
</tr>
<tr>
<td>RT-PCR (−)</td>
<td>108</td>
</tr>
<tr>
<td>Coinfection with HCV and HGV</td>
<td>0</td>
</tr>
</tbody>
</table>

*ELISA indicates enzyme-linked immunosorbent assay; RT-PCR, reverse transcription and polymerase chain reaction; plus sign, positive result; and minus sign, negative result.
†Discrepant results of RT-PCR; ie, 1 positive RT-PCR not confirmed by a second RT-PCR or by commercial standardized genomic amplification.

**OTHER FINDINGS**

Physical urticaria could be demonstrated in 11 patients: 9 had true urticarial dermographism, 1 had a strongly positive result on the ice cube test, and 1 had a positive result on the pressure test. All these findings were consistent with the history of urticarial symptoms reported by the patients.

Abnormal thyroid function was noted in 3 patients: 2 patients had hypothyroidism and 1 had hyperthyroidism. We found cryoglobulinemia in 1 patient who noticed the enhancement of urticaria after exposure to the cold. Nevertheless, the ice cube test gave a negative result. This patient had negative results on HCV tests (both ELISA and RT-PCRs). Antinuclear antibodies (>1:160) were found in 24 patients, but none of these patients had clinical symptoms of lupus erythematosus or other autoimmune diseases.

Serologic tests were positive for _T canis_ in 9 of 110 patients. Only 1 of them had hypereosinophilia and a high level of _Toxocara_ antibodies, and he was treated with albendazole. No improvement in cutaneous symptoms occurred after treatment. Serologic tests were positive for _H pylori_ in 23 patients.

**COMMENT**

This is the first prospective study that evaluated the prevalence of HCV and HGV infection in patients with chronic urticaria and in age- and sex-matched controls from the same geographic area.

The prevalence of HCV infection was not higher in patients with urticaria than in controls. Furthermore, the 0.9% prevalence is also close to that in the general French population (0.5%-1.0%). The interpretation of discrepant RT-PCR results can be difficult. In our study, using a sensitive RT-PCR method, false-positive results were obtained in both patients with urticaria and the control group. They could not be confirmed either by a second identical RT-PCR or by a standardized commercial
Table 2. Patients With Both Urticaria* and Hepatitis C Viral Infection

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients With Urticaria/Type</th>
<th>Urticaria Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reichel and Mauro,†1990</td>
<td>1†</td>
<td>Acute urticaria</td>
</tr>
<tr>
<td>Lin et al.‡1995</td>
<td>1†</td>
<td>Urticarial vasculitis</td>
</tr>
<tr>
<td>Raychaudhuri and Kaplan,‡1995</td>
<td>1†</td>
<td>Chronic urticaria</td>
</tr>
<tr>
<td>Kuniyuki and Katoh,‡1996</td>
<td>1†</td>
<td>Urticarial vasculitis</td>
</tr>
<tr>
<td>Kanazawa et al.,‡1996</td>
<td>15/58</td>
<td>Chronic urticaria</td>
</tr>
<tr>
<td></td>
<td>2/21</td>
<td>Acute urticaria</td>
</tr>
<tr>
<td>Smith et al.‡1997</td>
<td>0/50</td>
<td>Chronic urticaria</td>
</tr>
<tr>
<td>Llanos et al.‡1998</td>
<td>2/135</td>
<td>Chronic urticaria</td>
</tr>
<tr>
<td>Dourte et al.‡1998</td>
<td>1/50</td>
<td>Chronic urticaria</td>
</tr>
<tr>
<td></td>
<td>0/10</td>
<td>Acute urticaria</td>
</tr>
<tr>
<td>Dega et al.‡1998</td>
<td>5/27†</td>
<td>Urticarial vasculitis, 1; chronic urticaria, 4</td>
</tr>
<tr>
<td>Present study</td>
<td>1/110</td>
<td>Chronic urticaria</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

*There are probably some cases of urticarial vasculitis among series of patients with mixed cryoglobulinemia. This table lists those patients described in the literature whose urticaria is a presenting sign.
†Case report.
‡Selected patients seen by dermatologists because of chronic pruritus.

method; ELISA test results were also negative. Because all liver function test results were within the reference range and no risk factor for HCV could be elicited, the first positive RT-PCR result is likely to be due to contamination and was considered false positive.

The role of HCV infection in the 1 patient with urticaria and HCV antibodies is questionable because circulating RNA was not detectable either with the “homemade” method or with a commercial genomic amplification method. Urticaria occurring simultaneously with hepatitis A or B is thought to be due to circulating immune complexes.26 If this were the case in HCV infection, HCV RNA would also be detected. In this patient, no circulating immune complexes or changes in complement levels were found.

Our study shows that the systematic detection of HCV infection in a patient with urticaria is not valuable and certainly not cost-effective. Because the prevalence of HCV in this part of France is close to that in the present one, showed nonsignificant results. Few patients in the world literature have both urticaria and HCV infection (Table 2),7,11,13,29,31 except those with mixed cryoglobulinemia, who have urticarial vasculitis rather than true urticaria. On the other hand, in a previous study8 of a systematic cutaneous examination of 100 HCV-infected patients, none of the patients had present or past urticaria. It remains to be demonstrated, therefore, that there could be a significant link between urticaria and HCV.

These controversial results highlight the necessity of adequate control groups, derived from the same facility and during the same time period.

Acute urticaria occurring after HCV infection is likely to be relevant,11 and in 1993, a patient in whom severe urticaria developed associated with liver cytolysis was examined; after 4 weeks, HCV antibodies were demonstrated (B.J.C., unpublished data, 1993). Nevertheless, such cases are uncommon and rarely reported in the literature, suggesting that the link between urticaria and HCV is weak.

Because HGV shares the same route of transmission and belongs to the same family that HCV does, it was interesting to evaluate the rate of infection in the same group of patients. The prevalence of HGV was exactly the same in our 2 groups and was a little lower than the 4.2% prevalence among blood donors in France.32 It is unlikely that HGV could play a pathogenic role in urticaria because the prevalence was low and did not differ between the 2 groups. The role of HGV has also been ruled out in patients with lichen planus,22,33 but a slight increase in the prevalence of HGV was described in patients with porphyria cutanea tarda,34 as 8.9% of 124 patients had positive results on HGV tests. Nevertheless, the liver function test results in these patients did not differ from those of noninfected patients in the same study.34 The virus for hepatitis G could be “harmless,”35 but this remains controversial.20

Other investigations in our patients showed classic causes of urticaria, such as thyroid dysfunction and physical urticaria. The detection of Helicobacter and Toxocara species on serologic tests should be interpreted with caution. In previous experience, we could not obtain significant improvement of urticaria with the treatment of H pylori infection. The role of these organisms is still controversial, but the examination of this point was not a goal of the present study. Nevertheless, HCV and HGV infection rates were lower than the rate of, eg, thyroid dysfunction—an infrequent cause of urticaria—confirming that HCV screening does not seem to be useful.

CONCLUSIONS

The present case-control study shows that routine HCV testing is not cost-effective in patients with chronic urticaria. Although persistent infection with HGV is common, this disorder does not seem to be involved in urticaria.
REFERENCES