Increased Risk of Autoimmune Thyroid Disease in Hepatitis C vs Hepatitis B Before, During, and After Discontinuing Interferon Therapy

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Background: Thyroid gland dysfunction has been reported to occur with variable frequency during interferon alfa (IFN-α) therapy in patients with the hepatitis C virus (HCV). We prospectively evaluated if the prevalence of autoimmune thyroid disease in patients with HCV differs from that in patients with the hepatitis B virus (HBV) before, at the end of, and 6 months after stopping treatment with IFN-α.

Methods: One hundred thirty-four patients with HCV and 41 patients with HBV were studied. Measurements of serum free thyroxine, free triiodothyronine, thyrotropin, thyroid peroxidase antibodies (TPOAbs), thyroglobulin antibodies (TgAbs), and thyrotropin-binding inhibitory immunoglobulin were performed.

Results: Positive levels of TPOAb and TgAb were found in 20% and 11% of patients with HCV compared with 5% and 3% of patients with HBV, respectively. At the end of IFN-α therapy, thyroid gland dysfunction was more prevalent in patients with HCV (12%) compared with those with HBV (3%), with thyrotropin levels significantly higher in the HCV group (P = .03). Titers of TPOAb, TgAb, and thyrotropin-binding inhibitory immunoglobulin increased significantly (P = .02, P = .04, and P = .02, respectively) at the end of IFN-α therapy in patients with HCV but not in those with HBV. Patients who developed thyroid gland dysfunction were predominantly female (P = .03), had decreased levels of free triiodothyronine (P < .001), and had a higher prevalence of TPOAb (P = .03) before treatment with IFN-α. Thyroid gland dysfunction was reversed in 60% of those with HCV 6 months after discontinuing treatment with IFN-α.

Conclusions: Patients with HCV are more susceptible than patients with HBV to autoimmune thyroid disease. Systematic screening of thyroid gland function and TPOAb titers in all patients with HCV before, during, and after IFN-α therapy appears warranted. This precaution is not necessary for patients with HBV.

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HIGH PREVALENCE of thyroid gland dysfunction and/or antithyroid antibodies has been reported in patients with the hepatitis C virus (HCV) before1-3 or after4-7 therapy with interferon, and some data also show a high prevalence of anti-HCV antibodies in patients with autoimmune thyroiditis, suggesting that this condition could be induced by HCV infection.8,9 However, in most reports, no comparison has been made between chronic HCV infection and the other known types of chronic viral hepatitis (hepatitis B [HBV] and D). Therapy with interferon has important effects on the cell-mediated immune system as well as on many other immune mechanisms, such as the expression of major histocompatibility antigens10 and the regulation of cytokine production.11 Despite this broad range of immunological effects, the role of interferon alfa (IFN-α) in the pathogenesis of autoimmune thyroid disease remains uncertain. Autoimmune phenomena against the thyroid gland in patients with HBV infection are not well understood. We hypothesized that therapy with interferon may play a role in the development of autoimmune thyroid disease in patients with HBV in a manner similar to that which occurs in patients with HCV.

The aim of this prospective sequential study was to analyze whether the prevalence of autoimmune thyroid disease in patients with chronic active HCV is different from that in patients with chronic active HBV before, at the end of, and 6 months after stopping treatment with IFN-α.

RESULTS

BEFORE THERAPY WITH IFN-α

Subclinical hypothyroidism was found in 4% (5/134) of patients with HCV and none of the patients with HBV. None of the patients had clinical hypothyroidism or hyperthyroidism. Before treatment, positive levels of TPOAb and TgAb were found
PATIENTS, MATERIALS, AND METHODS

One hundred thirty-four patients with HCV (72 men and 62 women; mean age, 43 years; age range, 18-65 years) and 41 patients with HBV (27 men and 14 women; mean age, 32 years; age range, 17-56 years) were investigated in a prospective, sequential study. None of the patients had a history of thyroid gland dysfunction or were treated with thyroid hormones. The inclusion criterion was serologic evidence of HCV or HBV infection. A needle biopsy of the liver was used to confirm the diagnosis of chronic hepatitis without cirrhosis. All patients completed a therapeutic trial for 6 months with recombinant human IFN-α-2b (Intron A, Schering Plough, Levallois, France) self-administered by subcutaneous injection 3 times per week (3 megaunits for patients with HCV and 6 mU for patients with HBV). This study was approved by the local ethics committee and all study patients gave written informed consent.

METHODS

In all patients we measured serum levels of free thyroxine (FT₄) using a solid-phase antigen-linked radioimmunoassay (RIA-coat FT₄, Byk-Stangtec Diagnostica, Dietzenbach, Germany) (normal range, 10-36 pmol/L) and free triiodothyronine (FT₃) via radioimmunoassay (CIS Biointernational, Gif-Sur-Yvette, France) (normal range, 4.1-10 pmol/L). Ultrasensitive thyrotropin measurements were made via immunoradiometric assay (TSH-IRMA, CIS Biointernational) (normal range, 0.4-4.0 µIU/mL; lower limit of detection, 0.03 µIU/mL). Antithyroid peroxidase antibody (TPOAb) was assayed via radioimmunoassay (DYNO-test anti-TPO, Henning Laboratories, Berlin, Germany). Positive titers were considered those higher than 150 U/mL.12 Antithyroglobulin antibody (TgAb) was measured using radioimmunoassay (THYRAC-Assay, Henning Laboratories), and positive titers were considered those higher than 200 U/mL. Thyrotropin receptor-binding inhibiting immunoglobulin was measured via radioimmunoassay (TRAK-Assay, Henning Laboratories), with positive titers considered those higher than 15%.

Analyses were carried out before, at the end of, and 6 months after stopping therapy with IFN-α. Serum samples were kept frozen at -80°C. Subclinical thyroid gland dysfunction in terms of hypothyroidism or hyperthyroidism was considered present when the serum concentrations of thyrotropin were higher than 5.0 µIU/mL or lower than 0.03 µIU/mL, respectively, with normal levels of FT₄ and FT₃. Clinical hyperthyroidism was defined as an FT₃ value lower than 10 pmol/L and/or FT₄ value lower than 4.1 pmol/L and thyrotropin level higher than 4.0 µIU/mL.

STATISTICAL ANALYSIS

Results are expressed as mean ± SEM. Data were analyzed using the 2-tailed paired Student t test, χ² test, and analysis of variance, as appropriate. P < .05 was regarded as significant.

The prevalence of thyroid gland dysfunction at the end of therapy was 12% in patients with HCV and 3% in patients with HBV. Thyrotropin levels were significantly higher (P = .03) in patients with HCV than in those with HBV (5.1± 9.3 vs 2.2± 2.2 µIU/mL, respectively). There were also significant differences (P = .02) in thyrotropin levels from before to after treatment with IFN-α in patients with HCV but not in those with HBV (Table 1). In 4 patients with HCV, clinical hyperthyroidism was noted, and 2 patients became positive for thyrotropin receptor-binding inhibiting immunoglobulin. These 2 patients required antithyroid treatment for 6 months. Forty-four percent (12/27) of the patients with HCV testing positive for TPOAb before IFN-α therapy developed subclinical hypothyroidism after 6 months of IFN-α treatment, with a highly significant increase of their TPOAb titers (1.3 ± 5.0 vs 8.9 ± 9.34 U/mL; P < .001). Mean serum levels of TPOAb and TgAb increased significantly (P = .02 and P = .04, respectively) at the end of therapy with IFN-α in patients with HCV but not in those with HBV (Figure 2). Also, mean titers of thyrotropin receptor-binding inhibiting immunoglobulin increased significantly (1.8% ± 2.9% vs 2.9% ± 5.6%; P = .02) only in patients with HCV.

Patients with chronic active hepatitis who developed thyroid gland dysfunction at the end of therapy with IFN-α were predominantly female (P = .03), showed a significant decrease in mean levels of FT₃ (P < .001), and were positive for TPOAb (P = .03) before therapy with IFN-α (Table 2). Baseline aspartate aminotransferase levels and liver histological characteristics were not found to be statistically different when both groups were compared (P = .68 and P = .75, respectively).
Thyroid gland dysfunction reverted to normal in all patients with HBV and 60% of those with HCV 6 months after discontinuing treatment with IFN-α, although TPOAb results remained positive in 30% of patients with HCV. Anti-TPO levels (mean, 1215 ± 234 U/mL) remained positive in all patients with HCV, with permanent thyroid gland dysfunction following cessation of therapy with IFN-α.

This prospective study concerned 2 groups of patients with chronic active viral hepatitis (HCV and HBV) investigated before, at the end of, and 6 months after stopping therapy with IFN-α. The purpose of this study was to analyze differences in markers of autoimmunity between patients with HCV and those with HBV to determine whether treatment with IFN-α may induce thyroid autoimmunity differently in the 2 diseases.

In previous reports, the prevalence of abnormal concentrations of antithyroid antibodies in patients with chronic HCV varied markedly, ranging from 2% to 48%. Differences in geographical distribution, genetic variability in the populations studied, and even environmental factors, such as iodine intake or virus infection, could play a major role in the development of clinically recognizable autoimmune thyroid disease. Recently, we found information in the literature about the prevalence of thyroid autoantibodies and thyroid gland dysfunction before and after IFN-α therapy in patients with HBV, HCV, and hepatitis D. In that study, the highest rates of thyroid autoantibodies and of hypothyroidism (20.2% and 5.6%, respectively) were detected in the subset of women with chronic HCV infection.

Before therapy with IFN-α, we found a higher prevalence of thyroid gland dysfunction in patients with chronic active HCV compared with those with HBV. These results are in agreement with findings of Preziati et al. However, they found a prevalence of 4% in patients with HBV, while none of our patients presented with thyroid gland dysfunction prior to receiving IFN-α. Our autoantibody findings agree with those of Pateron et al, who found a prevalence of 11% for antithyroglobulin antibodies and 8% for antimicrosomal antibodies in patients with HCV. Tran et al demonstrated that the prevalence of antithyroid antibodies is greater in patients with HCV than in those with HBV (12.5% vs 2%) using the determination of TPOAb as a more sensible and specific method than the classic passive hemagglutination of antimicrosomal antibodies.

Our study clearly demonstrates that patients with HCV develop autoimmune thyroid disease more frequently than patients with HBV before and after completion of IFN-α therapy. This finding may be attributed partially to the high prevalence of TPOAb and TgAb in patients with HCV (20% and 11%, respectively) before treatment with IFN-α, compared with the levels recorded in patients with HBV (5% and 3%, respectively).

Table 1. Serum Levels of Thyroid Hormones in Patients With HCV and HBV Before and After Therapy With Interferon Alfa*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HCV Before Therapy</th>
<th>HCV After Therapy</th>
<th>HBV Before Therapy</th>
<th>HBV After Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free triiodothyronine, pmol/L</td>
<td>7.2 ± 1.2</td>
<td>7.7 ± 5.6</td>
<td>7.2 ± 1.3</td>
<td>7.3 ± 1.1</td>
</tr>
<tr>
<td>Free thyroxine, pmol/L</td>
<td>20.2 ± 5.2</td>
<td>20.5 ± 7.8</td>
<td>20.2 ± 3.9</td>
<td>19.5 ± 5.2</td>
</tr>
<tr>
<td>Thyrotropin, µIU/L</td>
<td>2.5 ± 7.7</td>
<td>5.1 ± 9.3†</td>
<td>1.6 ± 0.7</td>
<td>2.2 ± 2.2†</td>
</tr>
</tbody>
</table>

*HCV indicates hepatitis C virus; HBV, hepatitis B virus. All values are presented as mean ± SEM.
†P = .02 vs patients with HCV before therapy.
‡P = .03 vs patients with HCV after therapy.

Table 2. Clinical Data Before Therapy With Interferon Alfa in Patients With Chronic Active Hepatitis*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients Without Thyroid Gland Dysfunction</th>
<th>Patients With Thyroid Gland Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>149 (85)</td>
<td>26 (15)</td>
</tr>
<tr>
<td>Age, y</td>
<td>39.1 ± 13.1</td>
<td>38.1 ± 13.4</td>
</tr>
<tr>
<td>Sex, male-female ratio</td>
<td>91:58</td>
<td>8:18‡</td>
</tr>
<tr>
<td>Free triiodothyronine, pmol/L</td>
<td>6.1 ± 2.7</td>
<td>2.9 ± 3.6‡</td>
</tr>
<tr>
<td>Free thyroxine, pmol/L</td>
<td>19.5 ± 3.9</td>
<td>18.2 ± 3.8</td>
</tr>
<tr>
<td>Thyrotropin, µIU/L</td>
<td>1.6 ± 0.8</td>
<td>4.0 ± 13.4</td>
</tr>
<tr>
<td>TgAb, U/mL</td>
<td>44.9 ± 192.7</td>
<td>89.1 ± 187.1</td>
</tr>
<tr>
<td>TPOAb, U/mL</td>
<td>40.1 ± 135.4</td>
<td>332.8 ± 872.4‡</td>
</tr>
<tr>
<td>Thyrotropin receptor-binding inhibitory immunoglobulin, %</td>
<td>1.7 ± 2.8</td>
<td>0.4 ± 1.4</td>
</tr>
</tbody>
</table>

*All values are presented as mean ± SEM unless noted otherwise. TgAb indicates thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.
†P < .05.
‡P = .001.
In accordance with other reports, antithyrotropin receptor autoantibodies were undetectable in both groups before IFN-α therapy, and increased significantly after IFN-α therapy only in those patients with HCV. The explanation for a higher incidence of autoimmune thyroid disease and its worsening after IFN-α therapy in patients with HCV is unclear. Several hypotheses may be entertained, although the most plausible would be that HCV could initiate autoimmune thyroid disease by mimicking the structure of some component of thyroid gland tissue.

The outcome of thyroid gland dysfunction after discontinuation of IFN-α therapy has not been closely monitored in most series. We found that almost one third of patients with HCV continued to have thyroid gland dysfunction after stopping IFN-α therapy, and all patients were positive for TPOAb before treatment. Therefore, the patients most vulnerable to autoimmune thyroid disease appear to be those with an autoimmune response initiated prior to IFN-α therapy. Sustained hypothyroidism has been described20, however, Baudin et al21 found a complete recovery of thyroid gland function in all patients with HCV after withdrawal of IFN-α treatment. In our series, thyroid gland dysfunction was completely reversible in patients with HBV. Thus, patients with HBV appear to be able to suppress the autoimmune response on cessation of IFN-α therapy, whereas patients with HCV may not.

All patients with chronic active hepatitis who developed thyroid gland disorders had elevated levels of antithyroid autoantibodies before treatment with IFN-α and these stayed elevated after stopping treatment, confirming that preexisting autoimmunity is a risk factor for thyroid gland dysfunction.22,23 We also found female sex to be another risk factor for developing autoimmune thyroid dysfunction, although some dispute this finding.24 Another interesting feature not previously reported is the relationship between the lower FT3 levels before therapy and thyroid gland dysfunction. The pathogenic mechanism implicated in part may be a direct in vivo inhibitory effect of IFN-α on the synthesis and secretion of thyroid hormones, as shown by Yamazaki et al.25 Thus, the patients with HBV recovered thyroid gland function on cessation of IFN-α therapy. However, patients with HCV appear to have specific immunologic perturbations that result in persistent autoimmune thyroid disease prior to and despite cessation of IFN-α therapy.

Patients with HCV are more susceptible to autoimmune thyroid gland dysfunction than those with HBV both before and after treatment with IFN-α. Female sex, lower FT3 levels, and positive thyroid autoantibody titers before therapy are risk factors for autoimmune thyroid gland dysfunction in patients with chronic active hepatitis treated with IFN-α.

In patients with HBV, recovery of thyroid gland function is complete, indicating only a minor effect of IFN-α on the immunoregulatory mechanisms. Therefore, in terms of cost-effectiveness, patients with HCV should be screened for anti-TPO antibodies before IFN-α therapy and those with positive titers should have long-term follow-up of thyroid gland function. We do not recommend the screening of thyroid autoantibodies before and during IFN-α therapy in patients with HBV.

CONCLUSIONS

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