

Original Research Article

Thyroid function in chronic hepatitis C patients treated with interferon

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Abstract

Purpose: To investigate the effect of interferon (IFN) treatment for chronic hepatitis C (CHC) patients on thyroid function.

Methods: 65 patients (27 males and 38 females, aged 28 - 61 years) with mild or moderate CHC and early fibrosis admitted to Second Hospital of Lanzhou University from January 2017 to January 2018 were enrolled in this study, while 65 healthy subjects served as the control group. The study group received 135µg peginterferon alfa-2a injection (Pexosin) subcutaneously, once a week for 48 weeks. Ribavirin was administered orally once a day at doses ranging from 10 - 15 mg/kg body weight. Chemiluminescence immunoassay was used to measure thyroid hormone and antibody levels in both groups.

Results: After interferon therapy, the positive expressions of TGAb and TPOAb in the study group were lower than the corresponding values observed before treatment ($\chi^2 = 8.188$, $p = 0.004$; $\chi^2 = 11.527$, $p < 0.001$). Thyroid hormone levels in the study group were normal before treatment, but free triiodothyronine (FT3) and free thyroxine (FT4) were significantly lower in the study group ($t_1 = -9.58$, $t_2 = -14.61$, $p < 0.001$). However, FT3 and FT4 significantly increased after treatment in the study group, relative to the control group ($p < 0.05$). The level of TSH in the study group was significantly higher than the level before treatment ($p < 0.05$), but gradually returned to normal.

Conclusion: Chronic hepatitis C patients may have thyroid dysfunction, and IFN therapy may result in transient disorder in thyroid hormone metabolism. Thus, TSH, TGAb and TPOAb can be used as predictors of thyroid disease development during IFN therapy for CHC.

Keywords: Chronic hepatitis C, Thyroid hormone, Anti-thyroid autoantibody, Interferon

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INTRODUCTION

Hepatitis C is a common viral hepatitis caused by hepatitis C virus (HCV) infection. It is a chronic disease often associated with autoimmune damage and extrahepatic lesions such as thyroid abnormalities [1,2]. It has been reported that

approximately 71 million people (about 1 % of the world's population) have CHC infection, out of which more than 39,000 people die each year from HCV-related liver disease [3]. Chronic hepatitis C is one of the common causes of liver cirrhosis and hepatocellular carcinoma. There are about 5.6 million cases of hepatitis C in

China. According to the World Health Organization, 7 % of patients with CHC were treated worldwide by 2015 [4].

The World Health Organization (WHO) has set a goal to achieve 80 % cure of CHC by 2030 and eliminate HCV [5]. Studies have shown that HCV easily develops into CHC, and then necrosis and fibrosis, as well as complications such as upper gastrointestinal bleeding, ascites infection of the abdominal cavity, and hepatic encephalopathy [6]. In addition, severe cases can develop into cirrhosis and hepatocellular carcinoma, which severely affect the patient's physical and mental health [6]. Since 2014, all oral, direct-acting antiviral drugs (DAAs) used in the treatment of CHC have high response rates, short duration of treatment, and fewer side effects [7,8].

Prior to the development of DAA, the main treatment for chronic hepatitis C in China was IFN combined with ribavirin. However, IFN produces many adverse reactions in the treatment of chronic viral hepatitis, especially thyroid disease with incidence of 1.9 - 40.0 % [9,10]. Studies have shown that CHC patients are prone to thyroid disease, which can be aggravated by IFN therapy [11,12]. The present study was carried out to investigate changes in thyroid hormone and thyroid autoantibodies before, during and after antiviral therapy in patients with CHC. It was also aimed at analyzing changes in thyroid function before and after treatment so as to study the effect of antiviral therapy on thyroid function and its clinical significance.

EXPERIMENTAL

General information on subjects

Sixty-five patients with mild or moderate chronic hepatitis C, and early liver fibrosis admitted to Second Hospital of Lanzhou University from January 2017 to January 2018 were included in the study group. The clinical diagnosis was based on the 2015 guidelines for the prevention and treatment of chronic hepatitis C. They comprised 27 males and 38 females, aged 28 - 61 years, with a median age of 40.73 ± 8.48 years. All patients had a history of blood products, which were confirmed by quantitative analysis of hepatitis C antibody and HCV RNA. Patients with other underlying diseases were excluded. Sixty-five healthy subjects were selected as the control group. These comprised 24 males and 41 females aged 30 - 63 years, with a median age of 42.66 ± 9.31 years old. There were no significant difference in gender

and age between the two groups ($\chi^2 = 0.290$, $t = -1.24$, $p > 0.05$).

Treatment

The study group received 135 μ g peginterferon alfa-2a injection (Peginteron) subcutaneously, once a week for 48 weeks. Ribavirin was administered orally once a day at doses of 10 - 15 mg/kg body weight. During the course of treatment, adverse reactions in patients were carefully monitored. Patients who were forced to discontinue due to severe myelosuppression, psychiatric symptoms, and autoimmune diseases were excluded. This research was approved by the Ethical Committee of Second Hospital of Lanzhou University (approval no. 20174617) and carried out according to the Declaration of Helsinki promulgated in 1964 as amended in 1996 [13].

Observation indicators

Blood (3 mL) was taken from patients before and 6 months after the antiviral treatment, and 3 months after the termination of treatment in the study group. In addition, 3 mL fasting blood was taken from patients in the control group. The blood samples were allowed to clot, and the sera were used for the assay of FT3, FT4, TSH, TGAb, and anti-TPOAb with German Siemens Chemiluminescence Immunoassay Analyzer kits (ADVIA Centaur XP) in accordance with the manufacturer's protocol.

Statistical analysis

Statistical analyses were carried out using SPSS 17.0 statistical software. Measurement data were expressed as mean \pm standard deviation (SD), and t -test was used for comparison between groups. Count data was expressed as percentage (%), and compared between groups using chi square (χ^2) test. Variance analysis was used for comparison between groups, while LSD t -test was used for comparison within groups. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Positive expressions of TGAb and TPOAb

There were 17 cases of thyroid disease (26.15 %) in the study group, comprising 11 hyperthyroidism and 6 hypothyroidism patients. All patients were diagnosed after endocrine consultation, and symptomatic treatment was given, followed by IFN treatment.

Table 1: TGAb and TPOAb expression levels before and after treatment in the study group [n (%)]

Case	N	TGAb		TPOAb	
		Before treatment	After treatment	Before treatment	After treatment
Hyperthyroidism	11	9 (13.85)	2 (3.08)	10 (15.38)	1 (1.54)
Hypothyroidism	6	5 (7.59)	1 (1.54)	3 (4.62)	0
Total	17	14 (21.54)	3 (4.62)	13 (20.00)	1 (1.54)

* $P < 0.05$, compared with value before treatment

In the study group, the positive expressions of TGAb and TPOAb before treatment were 21.54 % (14/65) and 20.00 % (13/65), respectively, while in the control group, expressions of TGAb and TPOAb were 0 and 6.15 % (4/65), respectively. There were significant differences in the degree of expressions of TPOAb between the two groups ($\chi^2 = 15.690$, $p < 0.001$; $\chi^2 = 5.482$, $p = 0.019$). After treatment, the positive expressions of TGAb and TPOAb in the study group were significantly lower than those before treatment ($\chi^2 = 8.188$, $p = 0.004$; $\chi^2 = 11.527$, $p < 0.001$). These results are shown in Table 1.

Thyroid hormone levels

The thyroid hormone levels in the study group were within the normal range before treatment, but FT3 and FT4 were significantly lower than their corresponding values in the control group ($t_1 = -9.58$, $t_2 = -14.61$, $p < 0.001$; Table 2). However, FT3, FT4, and TSH levels in the study group were significantly increased after treatment ($p < 0.05$), but TSH level gradually returned to normal with the treatment (Table 3).

Table 2: Thyroid hormone levels prior to treatment

Group	Cases	FT3 (pmol/L)	FT4 (pmol/L)	TSH (mU/ml)
Control	65	5.77 ± 0.48	16.11 ± 1.74	4.81 ± 0.44
Study	65	4.92 ± 0.53	12.36 ± 1.12	4.69 ± 0.50
<i>t</i>		-9.58	-14.61	-1.45
<i>p</i>		< 0.001	< 0.001	0.149

Values are expressed as mean ± SD

Table 3: Thyroid hormone levels before, during and after IFN treatment

Period	FT3 (pmol/L)	FT4 (pmol/L)	TSH (mU/ml)
Before treatment	4.92 ± 0.53	12.36 ± 1.12	4.69 ± 0.50
During treatment	5.11 ± 0.67	13.21 ± 2.89	9.77 ± 1.61
After treatment	5.48 ± 0.63	14.61 ± 3.33	4.51 ± 0.47
<i>F</i>	14.036	12.163	567.730
<i>P</i>	< 0.001	< 0.001	< 0.001

Values are expressed as mean ± SD; $p < 0.05$, compared with value prior to treatment

DISCUSSION

Hepatitis C virus (HCV) infection is often associated with extrahepatic autoimmunity, especially thyroid disease [14]. This study was carried out to investigate changes in thyroid hormone levels in 65 patients with chronic hepatitis C before treatment. It was found that the levels of FT3 and FT4 decreased significantly, when compared with the normal control group, while TSH levels did not differ from the normal control group. On one hand, it may be that the impairment of liver function in the study group patients with chronic HCV infection was slight, thereby producing no significant effect on the synthesis of TSH and thyroid-binding globulin. On the other hand, the significantly lower levels of FT3 and FT4 in the study group could be due to autoimmune thyroid disease (AITD) caused by CHC [15].

The results showed that a transient thyroid hormone disorder occurred during the IFN treatment, as evidenced by significant increase in TSH. This may be related to the aggravation of autoimmune thyroid disease during IFN treatment. A similar result has been reported in studies carried out outside China [16]. In addition, 17 patients in the study group developed thyroid diseases, i.e., hyperthyroidism and hypothyroidism. The positive expressions of TGAb and TPOAb in these patients were higher than those in the control group. Their expressions were also higher after IFN treatment. This may be due to the fact that thyroid cells induce their own intrinsic immune response to continuous HCV infection and/or long-term exposure to HCV protein, which in combination with the exogenous IFN, can activate IFN-stimulated gene expression, resulting in the observed thyroid inflammatory response or disease [17].

In addition, HCV infection is also likely to induce a variety of immune-related diseases including AITD, and it can also cause significant changes in TGAb and TPOAb. Thyroid function (including various thyroid hormones and antibody levels) in the study group was improved, with gradual recovery of liver function and timely symptomatic treatment of the IFN-induced thyroid diseases. Thus, the antiviral treatment results were not

affected, which is consistent with results obtained elsewhere [18-22]. Therefore, patients with chronic hepatitis C may have abnormalities in thyroid hormone and thyroid antibody levels. Thus, the pros and cons should be weighed before IFN treatment, and tests for thyroid hormone and thyroid autoantibodies should be done during routine examination. The results obtained in the present study indicate that these tests would be helpful for predicting the occurrence of thyroid disease during IFN treatment.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

This work was done by the authors named in this article and the authors accept all liability resulting from claims which relate to this article and its contents. The study was conceived and designed by Pan Zheng; Ma Dongmei, Pan Zheng collected and analysed the data; Ma Dongmei wrote the text and all authors read and approved the text prior to publication.

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