

Original Research Article

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Interferon-Alpha and Ribavirin-Induced Thyroid Dysfunction in Chronic Hepatitis C Egyptian Patients: Incidence and Association

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ABSTRACT

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Thyroid dysfunction (TD) represents an extrahepatic manifestation of chronic hepatitis C. This study aimed to assess TD incidence and association with disease severity, pretreatment viral load, pegylated interferon alpha 2a or 2b formulations and response to treatment in chronic hepatitis C patients treated with pegylated interferon alpha and Ribavirin. TD was prospectively evaluated in 226 euthyroid chronic hepatitis C Egyptian patients treated with pegylated interferon-alpha and Ribavirin for 48 weeks at weeks 0,4,12, 24, 36 and 48 of treatment and within 6 months after treatment using serum free thyroxine, thyroid-stimulating hormone. The disease severity and response to therapy were evaluated using METAVIR system and polymerase chain reaction test respectively. Twenty six treated patients (11.5%) developed TD (16 hypothyroidism, seven hyperthyroidism and three biphasic thyroiditis). 14 patients with TD achieved sustained viral response. 8/26 (30.8%) TD spontaneously reversed after treatment cessation and 18 cases required therapy. TD was not associated with pretreatment viral load, severity of liver fibrosis, interferon-alpha formulations or response to treatment. We conclude that Interferon-alpha and ribavirin therapy possibly induces TD in chronic hepatitis C patients. TD does not associate with pretreatment virological parameter, severity of liver disease or virological outcome.

Introduction

Hepatitis C virus (HCV) infection is a major global health problem. HCV is both a hepatotropic as well as a lymphotropic virus and chronic infection is known to be responsible for both hepatic and extrahepatic diseases (Zignego and Craxì, 2008 and Antonelli *et al.*, 2008). Thyroid dysfunction (TD) represents one of the commonest extrahepatic endocrine manifestations of chronic hepatitis C (CHC) (Martin *et al.*, 2014). It is generally speculated that HCV infection itself may perpetuate the immune cascade, which leads to the appearance of autoimmune thyroid disorders, especially in genetically predisposed subjects (Antonelli *et al.*, 2004 and Zignego and Craxì, 2008). In addition, several studies demonstrated that interferon- α (IFN- α) and ribavirin (RIB) combination therapy of chronic hepatitis C (CHC) induces or exacerbates thyroid dysfunction (Tomer *et al.*, 2007 and Hwang *et al.*, 2015). The incidence of TD during combination therapy has been reported to occur in 3.9% to 27.7% of patients, with a mean incidence of 12.1% (Tomer *et al.*, 2007; Andrade *et al.*, 2008; Antonelli *et al.*, 2009 and Hwang *et al.*, 2015).

The types of thyroid disorder also vary and can manifest either as clinical autoimmune thyroiditis i.e., Hashimoto's thyroiditis and Graves' disease or as non-autoimmune thyroiditis i.e., destructive thyroiditis and non-autoimmune hypothyroidism (Nadeem and Aslam, 2012).

The mechanisms causing this condition are still poorly understood. This condition may be the result of immune activation by interferon synergistically with Ribavirin. IFN- α also precipitates thyroiditis by direct thyrotoxic effects (Földes *et al.*, 2004).

Association of TD induced by antiviral therapy with the severity of disease and

response to treatment shows varying results in literature. Also, the relationship between TD and viral kinetics or virological outcome, as well as the effects of the pegylated form of IFN- α on the thyroid gland remains controversial (Andrade *et al.*, 2008 and Hwang *et al.*, 2015).

This study aimed to assess the incidence of thyroid dysfunction in Egyptian chronic hepatitis C patient during and after treatment with pegylated interferon and ribavirin and to assess interferon-alpha and ribavirin-induced thyroid dysfunction with the severity of disease on liver biopsy, pretreatment viral load, treatment formulations (PEG-IFN α -2a or 2b) and response to combination therapy.

Materials and Methods

Study Patients

This prospective study included 226 patients receiving treatment for CHC at the interferon unite in the center of cardiology and digestive system, Sohag and Hepatitis out-patient Clinic, Assiut University Hospital, Assiut, Egypt between January 2012 and May 2015. The study was approved by the local Ethics Committee and was conducted in accordance with the previsions of the Declaration of Helsinki. Informed consent was obtained from all the participants before enrollment.

Chronic hepatitis C diagnosed on the basis of persistently raised serum alanine transferase (ALT) more than 6 months, positive Hepatitis C Virus (HCV) antibodies, positive HCV RNA by Polymerase Chain Reaction (PCR), no cirrhotic ultrasonographic findings and positive histopathological findings on liver biopsy. Liver biopsies were scored by METAVIR system.

Eligible CHC patients had normal pretreatment TSH levels and received weekly injections of PEG-IFN α -2a or -2b plus ribavirin orally for 48 weeks, followed for 24 weeks after treatment. PEG-IFN α -2a was administered once a week at a daily dose of 180 μ g, and PEG-IFN α -2b was administered once a week at a daily dose of 1.5 μ g/kg of body weight. Ribavirin was orally administered daily in two divided doses (1,000 mg for \leq 75 kg, 1,200 mg for $>$ 75 kg). If indicated, dose adjustment or even therapy interruption were made according to manufacturers' recommendations.

Patients with TD before treatment initiation, co-infection with hepatitis B virus and/or HIV infection, other causes of chronic liver disease, decompensated liver cirrhosis, autoimmune, cardiac or pulmonary disease, currently using immunosuppressant and/ or steroids, pregnancy and alcohol abuse were excluded.

Serum HCV-RNA data were available before the initiation of treatment (qualitative and quantitative PCR assay) and at week 0, 4, 12, 24 and 48 of treatment, as well as 12 and 24 weeks after the end of treatment schedule (qualitative PCR assay). Patients were classified as responders if they achieved sustained virological response (SVR), defined as undetectable HCV-RNA at six months after completion of antiviral therapy. The remaining patients were categorized as non-SVR.

All patients were evaluated clinically, serologically (HCV-Ab and HCV-RNA), biochemically (thyroid function tests and liver function tests) and hematologically (complete blood count) at baseline. Body height and weight were recorded at the beginning of the study and the body mass index (BMI) was calculated. Routine biochemical and hematological tests were

performed using automated techniques. Serological markers for viral hepatitis were detected using routine commercially available enzyme immunoassays (Abbott Laboratories, Abbott Park, IL, USA). Serum HCV-RNA levels were measured by real-time polymerase chain reaction (PCR) assay (COBAS TaqMan, Roche Diagnostics), with a lower limit of detection of 20 IU/mL

Patients had been examined serially for thyroid functions at week 12, 24, 36, 48 of treatment and 24 weeks after treatment for CHC using thyroid stimulating hormone (TSH); reference range being 0.3-5.0 uIU/ml, serum-free thyroxine (FT4); reference range being 0.8-1.8 pg/ml and serum total triiodothyronine (free T3); reference range being 2.0-4.7 pg/ml were determined by radioimmunoassay (RIA) using an automated system Commander Parallel Processing Center (Abbott) machine. During baseline evaluation, detection of thyroid autoantibodies was deemed unnecessary in the presence of normal thyroid values. TD was defined as TSH level of either more than 4.0 (hypothyroidism) or less than 0.3 (hyperthyroidism) mU/L. According to these tests thyroid dysfunction were classified into:

1. Clinical hypothyroidism (elevated TSH with decreased levels of FT3 or FT4)
2. Subclinical hypothyroidism (elevated TSH with normal FT3, FT4)
3. Clinical hyperthyroidism (decreased TSH with elevated levels of FT3 or FT4)
4. Subclinical hyperthyroidism (decreased TSH with normal levels of FT3, FT4).
5. Biphasic Thyroiditis. Presence of hyperthyroidism at 12 weeks, followed by hypothyroidism at 24 weeks of therapy

Patients with TD were followed up and received appropriate therapy for hypo- or hyperthyroidism in some cases during the course of antiviral therapy.

Statistical Analysis

The statistical analysis was performed using statistical package for social sciences (SPSS) version 17.0 for Windows (SPSS, Inc., Chicago IL, USA). Continuous data were expressed as means \pm standard deviation (SD) and compared using Student's T test or Mann-Whitney U-test for normally or abnormally distributed data respectively. Categorical variables were expressed as percentage and compared using chi-square (χ^2) test and Fisher's exact probability test. For all analyses, P value of < 0.05 was considered significant.

Results and Discussion

A total of 226 CHC patients received INF and RIB were included in this analysis; 44 females and 182 males with a mean age of 41.2 ± 12.2 years. All recruited patients completed the treatment course. The demographic and biochemical characteristics of the study patients were shown in Table 1. None of the patients had TD within the first 12 weeks of treatment. TD discovered at week 24 of antiviral treatment in 13 (5.8%) patients. At week 36 of treatment, further seven patients developed TD, and six cases developed at the end of treatment (48 weeks after treatment initiation, Table 2). So, a total of 26 patients (11.5%) developed TD after the end of treatment (week 48) where, 16 patients had hypothyroidism, seven had hyperthyroidism and three cases had biphasic thyroiditis. On the other hand, subclinical TD represented the majority of cases (57.7%) while, subclinical hypothyroidism was found in eleven patients, four patients had hyperthyroidism

(Table 2). None of the patients with thyroid dysfunction had to discontinue INF therapy.

Six months follow up after cessation of therapy, 21/26 cases (80.8%) with thyroid dysfunction (13 hypothyroidism, 6 hyperthyroidism and 2 biphasic thyroiditis) had normalization of TSH (Table 3), where thyroid dysfunction returned to normal values spontaneously in 8 patients at the end of first 3 months of the follow up. In the remaining 18 patients, TD did not reverse spontaneously, and all of them needed appropriate therapy for hypo- or hyperthyroidism. After further 3 months follow up, 13 out of 18 patients had normal thyroid function and only 5 patients still had thyroid dysfunction. No new cases (late-onset TD) have been reported during three and six months follow up after the end of treatment.

Of 226 patients, 137 (60.6%) achieved SVR. According to the univariate analysis, euthyroid patients achieved SVR more frequently than TD patients but without statistical significance ($p = 0.452$). The univariate Analysis also showed that TD was not associated with PEG-IFN formulations, liver fibrosis, and pretreatment viral load. The findings of the univariate analysis were summarized in Table 1.

This study reports the frequency of thyroid dysfunction during antiviral combination therapy with PEG-IFN- α and RIB for HCV. We found the frequency of thyroid disease at the end of 48 weeks of combination therapy were 11.5%. These findings were in agreement with previous studies which reported that thyroid dysfunction between 3.9% and 27.7%, with a mean incidence of 12.1% in patients received IFN- α and RIB (Tomer *et al.*, 2007, Andrade *et al.*, 2008, Antonelli *et al.*, 2009 and Hwang *et al.*, 2015). The study also showed that the thyroid function returned to normal in

80.8% of them (30.8% spontaneously and 50% by treatment) and only 19.2% had persistent overt TD symptoms after the 6 month follow-up period. Complete recovery of thyroid function within a few months

after therapy withdrawal has been reported (Tran *et al.*, 2006). However, in most studies the reversal of TD was only partial (Deutsch *et al.*, 1997 and Carella *et al.*, 2002).

Table.1 Characteristics of Chronic Hepatitis C Patients Including those with and Without Thyroid Dysfunction

Characteristics	CHC patients (n= 226)	Patients without TD (n= 200)	Patients with TD (n= 26)	P-value
Age (years, mean ± SD)	41.2 ± 12.2	41.2 ± 12.3	41.7 ± 11.9	0.856
Sex (%)				
Males	182 (80.5%)	162 (81%)	20 (76.9%)	0.621
Females	44 (19.5%)	38 (19%)	6 (23.1%)	
Laboratory parameters (mean ± SD)				
Total bilirubin (mg/dl)	1.2 ± 5.6	0.6 ± 0.06	1.6 ± 3.2	0.324
Serum albumin (g/dl)	4.4 ± 0.6	4.4 ± 0.6	4.5 ± 0.5	0.302
AST(U/L)	49.8 ± 32.7	50 ± 33.9	41.3 ± 18.1	0.158
ALT (U/L)	58.7 ± 40.3	59.3 ± 42.2	54.1 ± 21.6	0.538
Viral load (log ₁₀ IU/ml)	2.9 ± 3.8	1.1 ± 2.9	2.5 ± 1.1	0.267
Necroinflammatory activity (%) (A0/A1/A2/A3)	2/104/105/15 (0.9/46/46.5/6.6%)	2/88/97/13 (1/44/48.5/6.5%)	0/16/8/2 (0/61.5/30.8/7.7%)	0.333
Stage of fibrosis (%) (F1/F2/F3/F4)	149/66/10/1 (66/29.2/4.4/0.4)	130/60/9/1 (65/30/4.5/0.5%)	19/6/1/0 (73.1/ 23.1/3.8%)	0.860
Treatment (%)				
PEG-INF alfa 2b	115 (50.9%)	100 (50%)	15 (57.7%)	0.460
PEG-INF alfa 2a	111 (49.1%)	100 (50%)	11 (42.3%)	
Treatment response (SVR, %)	137 (60.6%)	123 (61.5%)	14 (53.8%)	0.452

CHC: chronic hepatitis C; TD: thyroid dysfunction; SD: standard deviation; ALT: Alanine transaminase; AST: Aspartate transaminase; PEG-INF alpha: Pegylated Interferon alpha; SVR: sustained virological response

Table.2 Thyroid Dysfunction among Chronic Hepatitis C Patients during Treatment

Thyroid dysfunction	thyroid dysfunction during CHC treatment			Total (n= 26)
	Week 24 (n= 13)	Week 36 (n=7)	Week 48 (n= 6)	
Hypothyroidism	7 (53.8%)	5 (71.4%)	4 (66.7%)	16 (61.5%)
Subclinical	4	4	3	11
Overt	3	1	1	5
Hyperthyroidism	4 (30.8%)	1 (14.3%)	2 (33.3%)	7 (26.9%)
Subclinical	2	0	2	4
Overt	2	1	0	3
Biphasic thyroiditis	2 (15.4%)	1 (14.3%)	0	3 (11.5%)

CHC: chronic hepatitis C

Table.3 Thyroid Outcomes in Different Types of Thyroid Dysfunction for the Studied Patients at the End of 6 Month Follow up after Treatment

Thyroid outcome	Type of dysfunction				
	Hypothyroidism (n= 16)		Hyperthyroidism (n= 7)		Biphasic TD (n= 3)
	Subclinical	Overt	Subclinical	Overt	
Normalized (n=21)	10 (62.5%)	3 (18.75%)	5 (71.4%)	1 (14.3%)	2 (66.7%)
Still not normalized (n=5)	1 (6.25%)	2 (12.5%)	0	1 (14.3%)	1 (33.3%)

Several extrahepatic diseases have been associated with HCV, but thyroid disorders are the most common endocrinopathy, exacerbated by IFN- α and RIB treatment (Deutsch *et al.*, 1997). IFN-induced thyroid disease (IITD) exhibits features from both drug-induced thyroiditis and autoimmune thyroid disease. IFN-induced infiltration of immune cells in thyroid gland leads to inflammatory destruction in addition to cellular immune response. Both processes lead to direct toxic effect on thyrocytes and immunomodulation respectively, leading to IITD (Akeno *et al.*, 2011). Direct toxic effect on thyroid cells results in thyrocyte apoptosis, rupture of follicles and release of thyroid hormones (Huang *et al.*, 2006). The exact mechanism of immune modulation is not known but studies on thyroid follicle cell culture reveal that IFN- α , β , and γ induces TH-1 chemokines; CXCL-9 and CXCL-10 and TNF- α play synergistic role (Antonelli *et al.*, 2009). RIB is a nucleoside analogue with immunomodulatory effects that may stimulate the immune system alone or synergistically with IFN- α to cause thyroid disease via an autoimmune mechanism (Bini *et al.*, 2004).

Our study demonstrated a wide spectrum of thyroid diseases, ranging from overt hypothyroidism and hyperthyroidism, and biphasic thyroiditis until subclinical hypothyroidism or hyperthyroidism. TSH is the most sensitive marker of thyroid function that can detect both subclinical hypo- and hyperthyroidism (elevated or

decreased TSH, with normal FT4, respectively) (Andrade *et al.*, 2011). The rate of subclinical forms of thyroid dysfunction is significantly higher in patients treated with IFN- α for HCV (Duncea and Pepene, 2008). This study showed a higher frequency of subclinical TD (57.7%). These findings have been found by other investigators and suggest that combination therapy for HCV can be continued, even in those who develop overt thyroid disease (Hsieh *et al.*, 2000).

The association of thyroid disease with the liver disease severity shows varying results in the Literatures. Similar to our study, Morisco *et al.*, (2001) showed no significant differences between thyroid dysfunction patients and liver inflammation or fibrosis. However, Rodriguez-Torres *et al.*, (2008) demonstrated that patients with HCV and severe fibrosis are more prone to develop TD during treatment with IFN- α as compared to those with mild fibrosis. It should be pointed out that (96.2%) of our patients presented a stage of fibrosis equal to or below F2.

In our study, no significant association was found in treatment response (SVR) to IFN and ribavirin therapy with occurrence of TD (P value = 0.452). Morisco *et al.*, (2001) concluded that percentage of thyroid dysfunction in long-term responders was not significantly different compared to that in non-responders. In another study (Nadeem *et al.*, 2009), development of thyroid disease

was neither associated with dose of IFN nor virological response. Unlike Hwang *et al.*, (2015), that found significant association between thyroid disease and SVR. Also, we found that TD development is not related to pretreatment viral load as well as no association to PEG-IFN formulations. Several previous studies have reached similar conclusions (Dalgard *et al.*, 2002 and Kee *et al.*, 2005).

Our limitation was the absence of data concerning thyroid-specific autoantibodies at baseline. Screening of antithyroid antibodies was not included in the standard pretreatment evaluation of our study because, a few years ago, their detection in the presence of normal thyroid function (normal TSH, FT3 and FT4 levels) have not been considered a contraindication for antiviral treatment. There is a large body of evidence to show that TD occurs mainly in euthyroid patients with an underlying predisposition, such as the presence of thyroid-specific autoantibodies (Deutsch *et al.*, 1997 and Huang *et al.*, 2006). On the other hand, because this patient population consisted of Egyptian patients forming a homogenous one in terms of HCV genotype (predominantly genotype 4) we could not assess the association between genotype and TD.

In conclusion, interferon and ribavirin combination therapy has been found to be inducing thyroid disorders in patients with HCV infection. Pretreatment viral load, liver fibrosis, PEG-IFN- α formulations and virological outcome in treated patients do not influence development of DT in chronic HCV patients. Thyroid function tests should be screened before treatment and monitored during therapy regularly. The actual relevance of the TD to chronic HCV infection remains to be fully clarified in large prospective studies.

Conflicts of Interest

The authors declared that they had no conflicts of interest concerning this article.

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