

# Delta hepatitis-related thyroid disease: a unique phenomenon

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## Abstract

**Introduction:** Hepatitis delta virus (HDV) infection is a serious health problem worldwide. Thyroid disturbances represent a major limitation to the efficacy of interferon treatment targeting chronic HDV (C-HDV) infection. Moreover, pre-treatment thyroid diseases may be influenced by interferon therapy. Despite this, the characteristic features of the thyroid diseases in C-HDV patients remain poorly characterised.

**Aim:** To determine the prevalence of thyroid diseases and evaluate the impact of delta hepatitis on thyroid function tests.

**Material and methods:** We retrospectively reviewed the charts of 127 hepatitis C virus (HCV)-negative adults, treatment-naïve outpatients with C-HDV, between July 2013 and July 2014. Thyroid-stimulating hormone (TSH) and thyroid antibodies (TAb) including anti-thyroid peroxidase antibodies (anti-TPO), liver transaminases, and other routine laboratory tests were conducted during the study period.

**Results:** A total of 127 C-HDV patients (female 52.9%, mean age 54.5 ±8.01 years) were enrolled. The rate of hypothyroidism, defined as a TSH level above 10 IU/l, was 4.7%. No patient had hyperthyroidism. Both elevated levels of liver transaminases and HDV ribonucleic acid (HDV-RNA) were positively correlated with high levels of thyroid autoantibodies.

**Conclusions:** The rate of hypothyroidism is higher than the rate of hyperthyroidism at baseline. Most remarkably, for the first time we discovered a correlation between disturbed thyroid autoantibodies and elevated liver transaminases as well as high HDV-RNA levels even in euthyroid delta hepatitis patients. But in order to have an adequate understanding of such correlations, further studies are needed.

## Introduction

Hepatitis delta virus (HDV) is the smallest defective ribonucleic acid (RNA) virus in humans, and it is a topic of growing importance in the field of hepatology [1]. Hepatitis B virus (HBV)-associated HDV infection is one of the most important health problems in the developing world and it can cause life-threatening conditions including cirrhosis, liver failure, and hepatocellular carcinoma [2]. A high dose of recombinant standard interferon (IFN) is currently the standard anti-HDV therapy. It has been reported that sustained viral response (SVR) rates after at least 48 weeks of pegylated and standard IFN were close to 20% [3]. The side effects of IFN-based regimens are well established. These include headache, fatigue, arthralgias and myalgias, hepatic-decompen-

sation, depression, thrombocytopenia, neutropenia, flu-like syndrome, and deterioration of thyroid function tests [4].

There have been many studies and case reports about the effect of IFN-based therapies on thyroid function tests in hepatitis C virus (HCV) patients. Interferon-related side effects involving thyroid glands are usually associated with a self-limiting course but can cause overt thyroid diseases in persons with pre-existing thyroid disease [5, 6]. An association of hypothyroidism with IFN treatment has also been reported in many studies involving HBV patients [7], but no tests have been conducted among patients with C-HDV infection in whom the only treatment option is IFN. Furthermore, limited data exist regarding factors that predict thyroid disorders during C-HDV monotherapy with IFN.

It is therefore important to determine the baseline thyroid diseases before initiation of IFN treatment.

## Aim

The objective of this study will be to disclose the characteristic features of thyroid disorders in patients with C-HDV infection.

## Material and methods

### Study population

Patients between 17 and 80 years of age who had C-HDV infection were included in the study, provided that they did not have liver cirrhosis, were positive for HBsAg for at least 6 months, and were positive for anti-HDV antibodies for at least 3 months. The study was conducted on 127 treatment-naive delta hepatitis patients (57 females; mean age  $43.5 \pm 15.6$  years) between July 2013 and July 2014. Patients with decompensated cirrhosis as well as those with other liver diseases were excluded from the study. The levels of thyroid-stimulating hormone (TSH), free thyroxin (FT4), and thyroid autoantibodies (antithyroid peroxidase (anti-TPO) antibodies and anti-thyroglobulin (anti-Tg) antibodies) were measured in all patients at baseline.

### Methods

Anti HDV IgG and HBsAg levels were studied with Enzyme Linked Immunosorbent Assay (ELISA) using a Cobas 601 device (Roche, Germany). HBV-DNA was measured with an Artus HBV-DNA-QS-RGQ kit (24), and HDV-RNA was analysed with primer design one step Rt-PCR (Primer Design, U.K.) using a Rotor Gene Q Real time PCR (Qiagen, Germany) device. TSH, Free T4, AntiTPO, and antithyroglobulin antibody were measured with an Abbot Diagnostics Kit (USA) using a CI16200 device.

A TSH level above 10 MIU/l was accepted as hypothyroidism. A TSH level lower than 0.3 MIU/l was accepted as a hyperthyroid state. The reference interval for FT4 was 1.6 to 1.8 ng/dl. Normal range for TSH was 0.4 to 4.5 MIU/l. The study was approved by the ethics committee in our institution.

### Statistical analysis

Statistical software package R (version 2.10.1 R, Foundation for Statistical Computing) was used for all analyses. Differences in patient characteristics were assessed with  $\chi^2$  tests and *t*-tests for categorical and continuous factors, respectively. Correlation between parameters inside the study group was assessed by Pearson correlation test.

## Results

Baseline demographic and disease characteristics of the study patients are shown in Table I. The majority of patients were male, with an overall mean age of  $43.5 \pm 15.6$  years. Of those patients initially identified as anti-HDV positive, only 4.72% (6 patients) had overt hypothyroidism. There was no patient with hyperthyroidism.

The overall prevalence of anti-TPO among study patients was 19.7%, with no significant differences between males and females. Among laboratory parameters, the only significant difference noted was that high serum levels of transaminases were associated with elevated levels of thyroid autoantibodies ( $p < 0.005$ ). Higher levels of HDV-RNA were also significantly associated with anti-TPO ( $p < 0.005$ ).

## Discussion

Hepatitis D virus is a defective small hepatotropic RNA virus and the virus needs HBV for replication. It has been shown that chronic HBV and HDV co-infection causes more severe liver damage than chronic HBV infection alone [8]. The highest HDV prevalence is seen in the Mediterranean Basin, parts of southern America and eastern Europe [9, 10]. Chronic hepatitis D virus infection (CHD) affects approximately 20% of individuals with hepatitis B infection in the eastern part of Turkey, ultimately leading to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) [11].

Despite recent progress in many liver diseases, treatment of HDV infection remains poorly developed. With large increases in HDV infection diagnoses in recent decades and advances in IFN therapies, more delta hepatitis patients are receiving IFN than ever before. However, current anti-viral therapy with IFN results in SVR rates of nearly 25% in patients with C-HDV infection [12].

Treatment with IFN-based regimens is associated with side effects and is contraindicated by numerous comorbid conditions. There is also strong evidence for an association between IFN therapy and autoimmune thyroid diseases. The IFN therapy may cause autoimmune thyroiditis with either hypothyroidism or hyperthyroidism, especially in predisposed patients [13].

Thyroid disorders in HDV patients is also a neglected issue. Guidelines do not include recommendations about thyroid screening for patients with C-HDV because only limited data are available. Presently there are also no definitive data on basic thyroid status for patients with C-HDV who can cope with IFN therapy [14, 15].

The spectrum of IFN-related side effects includes hyperthyroidism and hypothyroidism, which can cause disruption or modulation of the treatment. The pres-

ence of pre-treatment thyroid autoantibodies is being implicated in thyroid disorders during IFN therapy [16].

It has been concluded that hypothyroidism is more prevalent than hyperthyroidism in people with C-HDV infection and may cause therapy-related side effects. Additional work has identified the importance of thyroid autoantibodies that increase the risk of development of thyroid disease during IFN treatment; however, the factors that drive thyroid disturbance are still largely unknown [17].

In our study the rate of hypothyroidism was similar to previous IFN trials, with the current data showing less hyperthyroidism. We therefore concluded that patients with delta hepatitis should firstly be screened for thyroid function tests in terms of hypothyroidism.

C-HDV infection is also associated with a variety of different autoantibodies. Smooth muscle antibodies (SMA), basal cell layer antibodies (BCLA), stellate epithelial cell antibodies (SECA), thymic reticular cell antibodies (TRA), perithymocytic cell antibodies (PTA), anti-calmodulin antibodies, antinuclear antibodies (ANA), anti-lamin C antibodies, and liver-kidney microsomal antibodies may manifest themselves in the case of delta hepatitis [18–20]. Recent studies demonstrate a high frequency of thyroid autoantibodies in both hepatitis C and delta hepatitis patients [21]. We found a high rate of anti-TPO positivity in non-cirrhotic, treatment-naive delta hepatitis patients. Our data suggest that the presence of delta hepatitis may play a definitive role in driving and determining the mechanisms that contribute to autoantibody formation in this difficult-to-treat patient population. Additionally, there was a significant and positive association between thyroid autoantibodies and liver-related transaminases, suggesting that higher levels of transaminases may also reflect autoimmune thyroid diseases in patients with C-HDV infection. This data could be a diagnostic tool for the identification of patients with delta hepatitis, who are at risk of IFN-related thyroid disturbances. These results are also in line with the concept of an association between autoimmunity and C-HDV infection.

Another finding that became the focus of our concern throughout our analyses was that TSH levels were inversely correlated with albumin levels. A possible explanation for this finding is that advanced stages of liver damage are associated with more disturbed thyroid functions. The finding indicates a role for delta hepatitis-related thyroid disorder.

In the current study, we also found that higher FT4 levels were also correlated with higher levels of transaminases. This phenomenon may be due to either thyrotoxic effect on liver tissue or advanced stage liver disease-related decreased T4 to T3 conversion.

**Table I.** Baseline demographic and disease characteristics of the study patients

Parameter	Mean $\pm$ standard deviation	Minimum	Maximum
Age	43.5 $\pm$ 15.6	11.00	80
Haemoglobin	14.51 $\pm$ 2.30	4.60	19.20
Leukocyte	6.62 $\pm$ 2.90	1.10	20.90
Platelet	189.19 $\pm$ 78.11	25	546
ALT	64.73 $\pm$ 220.82	6	2685
AST	68.42 $\pm$ 294.22	10	4083
Total bilirubin	1.01 $\pm$ 1.53	0.04	12.60
Direct bilirubin	0.62 $\pm$ 1.34	0.01	10.46
ALP	206.61 $\pm$ 139.78	1.11	852
GGT	62.89 $\pm$ 70.43	4.10	420.40
Globulin	3.42 $\pm$ 0.76	1.80	5.40
Albumin	4.11 $\pm$ 0.76	1.70	7.58
Total protein	7.46 $\pm$ 0.84	3.96	9.45
Brucella	39.11 $\pm$ 160.89	0.00	1280
HBeAg	52.62 $\pm$ 233.70	0.00	1539
TSH	2.49 $\pm$ 5.03	0.17	42.00
AFP	60.99 $\pm$ 302.42	0.40	2000
Anti-TPO antibodies	0.82 $\pm$ 1.77	0.00	6.93
Anti-TG	28.05 $\pm$ 87.82	0.72	292.81
FT4	1.14 $\pm$ 0.20	0.70	1.95

ALT – Alanine aminotransferase, AST – aspartate aminotransferase, GGT –  $\gamma$ -glutamyl transpeptidase, ALP – alkaline phosphatase, TSH – thyroid-stimulating hormone, AFP –  $\alpha$ -fetoprotein, anti-TPO antibodies – anti-thyroid autoantibodies, anti-TG – anti-thyroglobulin, FT4 – free-thyroxine.

There were several weak points of the study. Firstly, our data was based on a small and single-centre delta hepatitis patient group. Secondly, the lack of liver biopsy results resulted in the failure of a histopathological association between thyroid function tests and liver fibrosis. Finally, due to the retrospective nature of the study we were unable to obtain ultrasonographic data of the thyroid on the study patients to define autoimmune thyroid disease.

## Conclusions

C-HDV infection is associated with significant changes in thyroid functions. Postulated pathophysiological implications are related to the immunoreactive effect of the virus. Baseline characteristics in pre-treatment thyroid autoantibodies frequency may pose a significant hurdle for success of IFN therapies in chronic delta hepatitis patients. The higher rate of thyroid

autoantibodies in study patients with more advanced disease may reflect an emerging phenomenon that requires further investigation to determine the underlying causative factors.

In the last analysis, it would be much more tempting to say that further studies of immunologic interrelationships between delta hepatitis and thyroid functions might reveal novel diagnostic tools, means, and modes as well as therapeutic targets in the field of hepatology.

## Conflict of interest

The authors declare no conflict of interest.

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