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Hepatitis C Virus Infection is Probably Associated with Autoimmune Disorders and Malignancies but not with Autoimmune Thyroiditis

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In this study initially consecutive patients with Autoimmune Thyroiditis (AT) were taken in the Endocrinology Polyclinics. Beside that age and sex-matched patients with HCV infection and control cases were randomly studied in the Gastroenterology and Internal Medicine Polyclinics, respectively. One hundred and seventy-two patients with AT, 62 with HCV infection and 110 control cases were studied. AT was diagnosed in eight (12.9%) cases of the HCV infecteds' group and this ratio was 11.8% (13 cases) in the control group ($p>0.05$). Similarly, HCV infection was detected in one (0.5%) case of AT group and this ratio was 0.9% (one case) in the control group ($p>0.05$). Parallel to these results, prevalences of antithyroid peroxidase and/or antithyroglobulin antibodies were detected as 29.0% (18 cases) and 32.7% (36 cases) in the HCV infecteds' and control groups, respectively ($p>0.05$). As another face of the results, it was detected one case of monoclonal gammopathy of undetermined significance and one case of lichen planus in the HCV infecteds' group. As a conclusion, HCV infection may be associated with autoimmune disorders and malignancies but not with AT.

Key words: Hepatitis C virus, autoimmune thyroiditis, antithyroid peroxidase antibody, antithyroglobulin antibody

INTRODUCTION

There are many reports about associations of hepatitis C virus (HCV) infection with high prevalences of autoantibodies and mixed cryoglobulinemia, Sjogren's syndrome, non-Hodgkin's lymphoma (NHL) and membranoproliferative glomerulonephritis (MPGN) like autoimmune disorders and malignancies (Kawamoto *et al.*, 1993; Pawlotsky *et al.*, 1995). Because of observed thyroidal dysfunctions during alpha-interferon (IFN) therapy in patients with HCV-induced hepatitis (Marcellin *et al.*, 1995), many studies have been performed and high prevalences of antithyroid peroxidase (anti-TPO) and antithyroglobulin (anti-TG) antibodies and autoimmune thyroiditis (AT) were reported in cases with HCV infection, even prior to alpha-IFN therapy (Tran *et al.*, 1993). On the other hand, iatrogenic destruction of the gland and AT are the most common causes of hypothyroidism in society (Vanderpump *et al.*, 1995), mainly affecting middle-age and elder females. Thus an abnormal thyroid-stimulating hormone (TSH) concentration is usually accepted as a proof of AT in iodine-sufficient areas (Parle *et al.*, 1991). Patients may come with hypo- or hyperthyroidism and/or goiter and AT accounts for 40% of goiter cases in young adults (Rallison *et al.*, 1991). Main diagnostic criteria of AT is presence of anti-TPO and/or anti-TG Abs in serum. Although it has not been accepted universally, many studies were reported about the high prevalences of HCV infection in AT (Duclos-Vallee *et al.*, 1994), but the association between them is unclear, yet. The aim of present study to understand whether there is a significant relationship between HCV infection and AT.

MATERIALS AND METHODS

The study was performed in the Endocrinology, Gastroenterology and Internal Medicine Polyclinics of the Mersin University, Mersin and Baskent University, Adana, between January 2004 and March 2005. Initially consecutive patients were taken with SAT in the Endocrinology Polyclinics. TSH, free thyroxine (free T4), free triiodothyronine (free T3) and anti-TPO and anti-TG Abs were studied and AT was diagnosed by positivities of anti-TPO and/or anti-TG Abs together with an abnormal TSH concentration in serum. Enzyme-linked immunosorbent assay (ELISA) was used to detect the anti-TPO and anti-TG Abs. Normal ranges of TSH, free T4 and free T3 are accepted as 0.25-4.30 microunits mL⁻¹, 0.5-2.1 ng dL⁻¹ and 2.3-4.2 pg mL⁻¹, respectively. AT cases were subdivided as obvious hyperthyroidism (a

suppressed TSH value together with elevated free T4 and/or free T3 values), subclinical hyperthyroidism (a suppressed TSH value alone), subclinical hypothyroidism (an elevated TSH value alone) and obvious hypothyroidism (an elevated TSH value together with decreased free T4 and/or free T3 values). Additionally, thyroid ultrasonography was performed for the AT patients. Lymphocytic infiltration and disruption of the tissue architecture induced hypoechogenicity and micronodulation are used as the evidences of AT (Yeh *et al.*, 1996; Mazziotti *et al.*, 2003). Beside that age and sex-matched consecutive patients with HCV infection and control cases were studied in the Gastroenterology and Internal Medicine Polyclinics during the same period, respectively. Patients with previous IFN therapy at least for a period of six months were excluded. Antibody against HCV (antiHCV) was searched by ELISA (Abbott AxSYM HCV, version 3.0) and HCV RNA by polymerase chain reaction (Roche Cobas Amplicor HCV Monitor Test, version 2.0) methods and HCV RNA positivity was accepted as an indicator of HCV infection. Monoclonal gammopathy of undetermined significance (MGUS) was diagnosed by low M-protein levels in serum (<3 g dL⁻¹) and urine (<300 mg day⁻¹), normal levels of other serum immunoglobulins and a normal bone marrow examination in the absence of any lytic bone lesion or Bence Jones proteinuria. Dermatologic consultation was obtained for lichen planus (LP) and biopsies were taken. Comparison of proportions was used as the method of statistical analysis.

RESULTS

One hundred and seventy-two patients with AT, 62 with HCV infection and 110 control cases were studied. AT was diagnosed in eight (12.9%) cases of the HCV infected group and this ratio was 11.8% (13 cases) in the control group (p>0.05). Similarly HCV infection was detected in one (0.5%) case of AT group and this ratio was 0.9% (one case) in the control group (p>0.05). Parallel to these results, prevalences of anti-TPO and/or anti-TG Abs were detected as 29.0% (18 cases) and 32.7% (36 cases) in the HCV infected patients' and in the control groups, respectively (p>0.05). On the other hand, 152 of the AT patients were female (88.3%) and the mean age of the AT cases was 46.0±13.8 years (Table 1). Twenty-eight (16.2%) of the AT cases were diagnosed as obvious hyperthyroidism, 6.3% (11 cases) as subclinical hyperthyroidism, 35.4% (61 cases) as subclinical hypothyroidism and 41.8% (72 cases) as obvious hypothyroidism (Table 2). Additionally, the sensitivity of

Table 1: Comparison of the hepatitis C virus infected and autoimmune thyroiditis patients and control cases

Variables	AT* patients	p-value	Control cases	p-value	HCV† infecteds
Number	172		110		62
Mean age and range (year)	46.0±13.8 (22-83)	>0.05	47.3±12.3 (24-76)	>0.05	45.2±10.5 (34-68)
Female ratio	88.3% (152)	>0.05	86.3% (95)	>0.05	85.4% (53)
Prevalence of anti-TPO‡ and/or anti-TG Abs§range (year)			32.7% (36)	>0.05	29.0% (18)
Prevalence of anti-TPO Ab	85.4% (147)	<0.001	22.7% (25)	>0.05	24.1% (15)
Prevalence of anti-TG Ab	73.8% (127)	<0.001	19.0% (21)	>0.05	16.1% (10)
Prevalence of AT			11.8% (13)	>0.05	12.9% (8)
Prevalence of HCV infection	0.5% (1)	>0.05	0.9% (1)		

*Autoimmune thyroiditis †: Hepatitis C virus ‡: Antithyroid peroxidase antibody §: Antithyroglobulin antibody. Values in parenthesis show No. of cases

Table 2: Clinical presentation types of patients with autoimmune thyroiditis

Variables	Obvious hyperthyroidism	Subclinical hyperthyroidism	Subclinical hypothyroidism	Obvious hypothyroidism
Prevalence (%)	16.2 (28)	6.3 (11)	35.4 (61)	41.8 (72)

(%) values in parenthesis show numbers

Table 3: Ultrasonographic properties of patients with autoimmune thyroiditis

Variables	Thyroiditis	Thyroiditis plus partial hyperplasia	Thyroiditis plus MNG*	Thyroiditis plus solitary nodule	MNG	Normal
Prevalence (%)	59.3 (102)	3.4 (6)	10.4 (18)	4.0 (7)	12.2 (21)	10.4 (18)

*Multinodular goiter, Values in parenthesis show numbers

ultrasonography for AT was detected as 77.3% (133 cases) in the AT group (Table 3). As another face of the results, we detected one case of MGUS and one case of LP in the HCV infecteds' group.

DISCUSSION

The relationships between HCV infection and autoimmune disorders and malignancies were reported before (Gumber and Chopra, 1995). Even we had detected two NHL, two MPGN, one idiopathic thrombocytopenic purpura, one prolymphocytic leukemia, one asthma and one lichen planus in 55 HCV RNA positive patients in another study and the difference between the HCV RNA positive and negative groups according to the total numbers of immunological and malignant disorders other than cirrhosis and hepatocellular carcinoma was significant (Table 4) (Helvacı *et al.*, 2006). But only one case of MGUS and one case of LP were detected in the HCV infecteds' group and no other disorder could be detected, probably due to the younger mean age of cases studied here (45.2 vs 59.3 years). On the other hand, the relationship between HCV infection and autoimmune disorders of the thyroid, particularly Hashimoto's thyroiditis, has extensively been searched, but parallel to our results, there could be found no significant association in between (Metcalf *et al.*, 1997; Gorez *et al.*, 1997). Additionally, we could not found any higher prevalence of the thyroidal autoantibodies in the HCV infected cases parallel to the results of some other studies (Boadas *et al.*, 1995; Loviselli *et al.*, 1999). Although the cause of these differences is unclear yet, factors such as the heredity and iodine intake of the studied population may be the underlying reason.

Table 4: Comparison of HCV RNA positive and negative groups

Variables	HCV RNA positive group	HCV RNA negative group
No. and gender distribution	55.0 (29 females)	31.0 (18 females)
Mean age and range (year)	59.3±10.5 (39-87)	49.2±15.0 (14-77)
Cirrhosis	18	0
HCC†	5	0
NHL‡	2*	0*
MPGN§	2*	0*
ITP¶	1*	0*
PLL¶¶	1*	0*
Asthma	1*	0*
Lichen planus	1*	0*
MGUS**	0*	1*

*p<0.001 †: Hepatocellular carcinoma ‡: Non-Hodgkin's lymphoma. §: Membranoproliferative glomerulonephritis ¶: Idiopathic thrombocytopenic purpura. ¶¶: Prolymphocytic leukemia **Monoclonal gammopathy of undetermined significance

It is already known that alpha-IFN therapy may trigger developments of thyroidal autoantibodies and AT (Preziati *et al.*, 1995), particularly in the third month of the therapy and they disappear by withdrawal. But treatment should be withdrawn only in severe, especially hyperthyroidic cases. Alternatively, increased dosages of drugs during the antiviral therapy may be useful in patients already using thyroid medications and low titers of the autoantibodies are not a contraindication for the antiviral therapy. Therefore, it is recommended that thyroidal autoantibodies and TSH should be checked in all patients candidates for alpha-IFN therapy.

AT is actually an organ-specific disease, characterized by lymphocytic infiltration of the gland and production of autoantibodies directed against thyroid specific antigens. Tissue damage and progressive loss of thyroidal functions are the end results of this process. It is subdivided into Hashimoto's thyroiditis (chronic lymphocytic thyroiditis), Graves' disease and painless

thyroiditis, which is also called as postpartum thyroiditis. But we subdivided the AT patients as obvious or subclinical hypo- or hyperthyroidism in stead here, since progression from Graves' to Hashimoto's thyroiditis is now well-recognized and although being rare, the inverse may also occur. As a significant result of the study, the prevalences of AT and anti-TPO and/or anti-TG Abs were detected as 11.8% and 32.7% respectively in the control group here, which shows the already presenting very high prevalences of AT and thyroidal autoantibodies in society. In another word, nearly one third of population is positive for the antibodies and one in every eight adults is AT.

Beside the HCV infection, there are many disorders suspected to be related with the thyroidal autoantibodies and/or AT in literature, such as MPGN, multiple sclerosis, end-stage renal failure, elevated CA 19-9, acquired ichthyosis and hypertrichosis, diabetes mellitus and Crohn's disease (Valentin *et al.*, 2004; Vecino *et al.*, 2004; Niemczyk *et al.*, 2004; Parra *et al.*, 2005; Brazzelli *et al.*, 2005; Vondra *et al.*, 2005; Inokuchi *et al.*, 2005). Although most of these disorders are rare, the thyroidal autoantibodies and AT, in stead, are frequent in society as mentioned above. Thus during searching such relationships, searchers have to keep in mind the already found high prevalences of them in society.

As a conclusion, HCV infection may be associated with autoimmune disorders and malignancies, but not with AT and its suspected relationship with AT, probably as in most of the other disorders thought to be related with AT, comes from the already presenting very high prevalences of the thyroidal autoantibodies and AT in society.

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