The prevalence of autoimmune hepatitis in Hashimoto's thyroiditis in a turkish population

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Abstract

Purpose : **Hashimoto's thyroiditis (HT) is an autoimmune thyroid disorder. Although its etiopathogenesis is obscure, there are many findings about the relationship between other autoimmune diseases and HT. The reason for this association is a topic of interest, but in our study we searched for the concurrence of autoimmune hepatitis (AH) with HT, which is a relatively new autoimmune disorder for this association.**

Methods : **Forty-six patients (44 female, 2 male) with HT were included in the study. Liver function tests, viral hepatitis markers, autoantibody panels, ultrasonography and liver biopsy were performed in certain cases.**

Results : **All patients were hepatitis B negative, only two patients were hepatitis C positive (4.3%). Smooth muscle antibody (SMA) was 21.7% positive, ANA was 26% positive, Anti-Liver kidney microsomal antibody-1 (LKM-1) was 13.4% positive. Anti-mitochondrial antibody (AMA) was not detected. Liver biopsy performed on six patients. Two of them had (+++) positive LKM-1 antibody titer, the other two had ANA and SMA positive results respectively and the last two had chronic hepatitis C infection. The pathology revealed AH in first four patients. We found four out of forty-six patients with HT as AH (8.69%).**

Conclusion : **HT patients should be searched for autoimmune diseases and AH might be one of them.** (Acta gastroenterol. belg., **2002**, 65, **143-145**).

Key words : autoimmune hepatitis, thyroiditis, autoantibodies.

Introduction

HT was first described between years 1905-1909 (1). Thereafter, it was shown that the autoimmunity is playing major role in the etiopathogenesis of the disease and it is chronic thyroid gland pathology. HT sometimes coexists with other autoimmune diseases, such as Sjögren ' s syndrome, type IIb AH, systemic lupus erythematosus, insulin-dependent diabetes mellitus, Graves' disease, vitiligo and alopecia areata (2). Three major types of antibodies are synthesized in HT. These are anti-thyroglobuline, anti-peroxidase, and anti-thyroid receptor blocking antibodies. Autoimmune thyroiditis is also associated with the polyglandular autoimmune syndromes (PGOS). PGOS was defined as type I, II and III (3). Type II PGOS is related to HLA tissue compatibility antigens and includes Addison's disease, chronic autoimmune thyroiditis, and insulin-dependent diabetes mellitus. On the other hand, Type III is associated with autoimmune thyroiditis and sometimes with liver involvement (3). In a study concerning thyroid diseases, the prevalence of anti-hepatitis C virus antibody was higher in HT patients (4). AH, characterized by autoantibodies in the serum and hypergammaglobulinemia, was first described in 1951 (5). The structural formation of the AH has become more obvious with the progress in understanding the hepatitis C serology and definition of the autoantibodies in the serum. According to these data, AH was divided into four groups. Type I was defined with the presence of antinuclear antibody and anti-smooth-muscle antibody (SMA) positivity without any other autoantibodies. Type II was further divided into two groups according to the presence of C virus antibody. Type IIa includes liver-kidney microsomal antibodies (LKM1) whereas ; Type IIb was defined by the presence of the HCV-RNA positivity and LKM1 antibody. Type III was associated with high titers of soluble liver antigen (SLA) but low titers of SMA and antimitochondrial antibody (AMA) positivity (6). Except some case reports, we were unable to find any detailed study concerning HT with AH in the literature. The incidence of AH in the population was reported as 0.69 / 100000.The objective of this study is to determine the frequency of the AH in patients with HT.

Population and methods

Patients

The patients, who were admitted to Gazi University Medical Faculty Endocrinology and Metabolism outpatient clinics, were included in the study. Forty-six HT patients were enrolled in the study (44 female, 2 male). The mean age value of the patients was 39.6 ± 2.34 (19.0-66.0) years. There was no history of previous hepatitis, hepatotoxic drugs, alcohol intake, family history of liver disease in any of the cases. Serum ceruloplasmin, ferritin, transferrin saturation values were normal. Baseline characteristics of these patients are given in table 1.

Laboratory findings

Thyroid function tests were measured by chemiluminescent assay method ; anti-thyroglobuline and antimicrosomal antibodies were measured by radioimmunoassay

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Table 1. — **Baseline characteristics of HT patients (n = 46)**

Age (mean ± SE), range	39.6 ± 2.34 (19-66) years
Gender	2 female, 44 males
Duration of symptoms (mean ± SE), range	17.79 ± 3.72 (1-60) months
FreeT3 (1.2-2.9 pg/ml)	4.10 ± 0.53 (pg/ml)
FreeT4 (5-12 ng/ml)	9.13 ± 1.27 (ng/ml)
Total T4 (64-154 nmol/L)	61.6 ± 12.1 (nmol/L)
TSH (0.4-5 mU/ml)	25.6 ± 7.40 (mU/ml)
Anti-thyroglobulin antibody (Anti-T) (<100 IU/ml)	628 ± 270 (IU/ml)
Anti-microsomal antibody (Anti-M) (<100 IU/ml)	779 ± 142 (IU/ml)

method. The liver function tests, viral hepatitis markers, protein electrophoresis, serum IgG, ANA, AMA, SMA, Anti-DNA, LKM1 antibody, prothrombin time were measured in all patients. AMA, SMA, LKM-1 antibodies were studied by indirect immunofluorescence method.

Histopathology

Fine needle liver biopsy was performed in patients with high transaminase levels for more than 6 months and high autoantibody titers. Liver biopsies were evaluated for presence of piecemeal necrosis, lobular inflammation with or without bridging necrosis, rosetting of liver cells, biliary changes, hydropic swelling of hepatocytes, parenchymal collapse, portal lymphoid aggregates. Individual histopathological findings were graded on a scale of 0 to 3 according to severity (0, absent ; 1 mild ; 2, moderate ; 3, severe).

Diagnostic criteria

AH diagnosis is based on the International Autoimmune Hepatitis Group criteria : Female gender, serum biochemistry, increased serum IgG, autoantibody titers, absence of AMA, negative viral markers, negative history of recent hepatotoxic drug usage and alcohol intake, genetic factors, histology were considered.

The results are presented as mean ± standard error of the mean.

Results

All patients were HBsAg negative, and only two patients were HCV positive (4.3%). These patients were also HCV-RNA positive. Abdominal ultrasonography revealed six hepatosteatosis and two cases of cholelithiasis. Positive autoantibody rates were ANA 26% (12/46), SMA 21.7% (10/46), and LKM-1 13.4% (6/46). AMA was not detected. Four patients had abnormal values of liver function tests, albumin/globulin ratios, IgG levels. Two of them were LKM-1 antibody positive, the other two were SMA and ANA positive patients. Liver biopsies of these four patients revealed varying degrees of lobular inflammation with bridging necrosis, piecemeal necrosis, roset formation, hydropic swelling of hepatocytes. There were neither significant biliary changes, granulomas, marked plasma cell infiltrate, lymphoid aggregates nor any other changes suggestive of a different etiology. Protein electrophoresis showed decline in albumin fraction and an increment of the globulin fraction in six patients. Only four of these patients had AH according to International Autoimmune Hepatitis Group criteria, other two patients were HCV positive. Ig G values were also increased in this four AH patients.

Consequently, we found that four patients out of forty-six had AH (8.69%).

Discussion

Thyroid microsomal antibody, thyroglobuline and anti parietal antibodies are frequently found positive in Type II AH. Interestingly, LKM1 antibody, presenting with Type II AH, mainly inhibits the functions of P450IID6 cytochrome and causes the clinical picture (7). LKM1 antibody was also observed with chronic hepatitis C infection. Recent studies showed a relationship between the geographical distribution of the concurrence of LKM1 antibody and hepatitis C infection. (8). The studies also showed that the incidence of AH triggered by LKM1 antibody in chronic hepatitis C was between 0-5-percentage (8). Skillern *et al*. reported an increment of globulin and a decrease in albumin values in HT patients (9). Another study revealed Paget's disease in seven of 35 HT patients. In this study, the association of cirrhosis, hemolytic anemia and rheumatoid arthritis was also described and the fact that autoantibodies might attack various tissues was mentioned.

Table 2. — **Clinical, biochemical, serological and autoimmune parameters of all patients (n = 46)**

Fatigue, palpitation	40/46 (87%)
Asymptomatic	6/46 (13%)
AST (0-35 IU/L)	28.4 ± 4.9
ALT (0-35 IU/L)	25.8 ± 3.9
ALP (30-120 IU/L)	80.5 ± 5.4
GGT (0-50 IU/L)	21.7 ± 2.7
IgG (800-1500 mg/dl)	1914.1 ± 216
Globulin (2-3.5 g/dl)	3.7 ± 0.9
Albumin (3.5-5.5 g/dl)	3.6 ± 1.4
Number of HbsAg positive patients	0/46 (0%)
Number of HCV-Ab positive patients	2/46 (4.3%)
Number of HCV-RNA positive patients	2/46 (4.3%)
Number of patients with SMA> 1/40	10/46 (22%)
Number of patients with ANA> 1/80	12/46 (26%)
Number of patients with LKM-1 > 1/40	6/46 (13%)
Number of patients with AMA> 1/40	0/46 (0%)

Table 3. — **Liver function tests, radiologic and histopathological features of AH patients**

	Patient 1	Patient 2	Patient 3	Patient 4
AST/ALT (IU/L)	48/46	55/34	39/53	66/84
ALP/GGT(IU/L)	76/34	89/23	101/44	59/40
Albumin / Globulin (g/dl)	3.2/4.1	2.9/3.8	3.0/3.6	3.1/3.8
Ultrasonographic data				
• hepatosteatosis	+	+	+	+
• heterogenous echogenicity	+	+	+	-
Histopathology*				
• Piecemeal necrosis	2	3	1	2
• Bridging necrosis	1	1	0	1
• Lobular inflammation	3	3	2	3
• Parenchymal collapse	2	1	1	1
• Rosette formation	1	1	1	1
• Bile duct damage	0	0	0	0
• Hydropic swelling	1	1	2	1
• Portal lymphoid aggregate	0	0	1	0
• Cirrhosis	0	0	0	0
• IAHG score**	18	18	18	16

* Individual histopathological findings were graded on a scale of 0 to 3 according to severity (0, absent ; 1 mild ; 2, moderate ; 3, severe).

** International Autoimmune Hepatitis Group criteria.

The decrease in the albumin and increment in the alpha2, beta and gamma globulins were described in the serum protein electrophoresis of the HT patients. Nagai *et al*. discussed a HT patient with transient hypothyroidism AH and an isolated ACTH deficiency after stopping the glucocorticoid treatment (10). In this case, following discontinuation of 5 mg prednisolone treatment liver dysfunction and hypergammaglobulinemia occurred in two months. AST, ALT, GGT levels were high, but hepatitis A Ig G was positive and Ig M was negative. In addition, hepatitis B and C markers were negative. Anti-smooth muscle antibody (anti-smooth muscle antibody), microsome test (MCHA) and antithyroid antibodies were positive. Anti-Nuclear antibody, anti-DNA antibody, anti-mitochondrial antibody and anti-adrenocortical, anti-pituitary antibodies were negative. The case was investigated by similar endocrinologic parameters such as FT4, FT3, TT4, TT3, and TSH, anti-M, anti-T, thyroid fine needle aspiration biopsy. Since Addison's disease was absent, this case was defined as type III. It was reported that hepatitis B and D were more frequent than hepatitis C in patients with HT (11) PGOS is a clinical entity defined by multiple endocrinologic organ failure. It is classified as Type I, II and III (3). We did not perform any dynamic tests on study groups because there were neither sign nor symptoms of Addison's disease. However, all of them had HT. There was no relation between seasons and the diseases a result ; we could not reach large series in studies concerning HT. One of the studies in the literature reported 81 cases of AH and only two patients were found to have HT (2.46%) (12). Nevertheless, in our study, there was a concurrence of HT and AH at a rate of 8.69%. This was significantly higher than the values reported for the normal population in various studies ; 0.001% and 0.69 / 100000 (13, 14)

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