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Prevalence of HCV antibodies in autoimmune thyroid disease

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Abstract. – *Background and Objectives*: Auto-immune thyroid disease (AITD) has often been reported during interferon-alpha therapy for chronic viral C hepatitis (HCV) or other diseases. Recently, a high AITD prevalence has been reported in HCV independently on alpha-interferon therapy. The aim of our study is to investigate the possible relationship between AITD and HCV and HBV virus infections, and their influence on the thyroid function.

***Material and Methods*: We prospectively studied 112 patients with AITD (94 women and 18 men; mean age: 49.8 ± 14.9 yrs) and 88 patients with non-toxic goitre (NTG) (73 women and 15 men; mean age: 50.2 ± 13.5 yrs) as controls. In all patients HCV antibodies, HBsAg and anti-HBs antibodies, TSH, FT3 and FT4 serum levels, circulating anti-thyroid-peroxidase antibodies (TPO-Ab) and anti-thyroglobulin antibodies (TG-Ab) were measured.**

***Results*: HCV antibodies were positive in 11.6% of AITD patients (13/112) and in 2.3% of controls (2/88) ($P < 0.05$), the prevalence of HCV in the controls being similar to the expected value in the general population (about 2%). HBsAg and anti-HBs were found only in 2.6% of AITD patients (3/112) and 1.1% of controls (1/88) (P = NS), according to the expected value in the general population (about 2.5%). No difference in thyroid function was observed between positive and negative HCV subgroups.**

***Conclusion*: A significant association between HCV infection and AITD was found. This finding confirms that HCV, but not HBV, could be one of the environmental factors responsible for the breakdown of immunological tolerance. Therefore detection of TPO-Ab and TG-Ab in all HCV patients, independently of IFN therapy, is suggested and the utility of a screening for HCV in all AITD patients is stressed.**

Key Words:

Autoimmunity, Thyroid, Viral C hepatitis.

Introduction

Auto-immune thyroid disease (AITD), like most other autoimmune disorders, is the result of a complex interaction between genetic, endogenous and environmental factors[1]. In the past, the occurrence of AITD during alpha-interferon (α-IFN) administration for chronic viral C hepatitis (HCV) or other diseases was often reported[2-4]. However, recent studies have shown a high prevalence of anti-thyroid antibodies in patients with HCV, also before IFN-treatment, suggesting that AITD could be induced by HCV infection[5-8]. Therefore, HCV may be one of the environmental factors involved in the development of AITD in genetically predisposed individuals[9]. HCV infection is associated with various extra-hepatic disorders as mixed cryoglobulinemia, porphyria cutanea tarda and membrano-proliferative glomerulonephritis[10].

Various mechanisms have been proposed to explain autoimmunity induction by HCV, as the ability of inducing an α-IFN response[7]. The results of studies carried out in AITD patients are discordant. Some data show a high prevalence of HCV antibodies in AITD patients, confirming the hypothesis that this condition could be induced by HCV infection[11,12]. On the other hand, no evidence of an epidemiological association of thyroid autoantibodies and HCV was found in other studies[13,14]. Most studies were carried out in HCV positive patients and in these reports the prevalence of anti thyroid antibodies varied markedly, ranging from 2% to 31%[15,16].

The aim of our prospective study is to investigate the prevalence of HCV and HBV antibodies in patients with AITD and to assess their influence on the thyroid function.

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Patients and Methods

Between November 2003 and June 2005, we enrolled 112 consecutive patients with AITD (94 women and 18 men; mean age: 49.8 ± 14.9 yrs) and 88 patients with non-toxic goitre (NTG) (73 women and 15 men; mean age: 50.2 ± 13.5 yrs) as controls. All patients and controls were studied in the outpatients clinic of Endocrinology at Policlinico A. Gemelli in Rome, Italy. The inclusion criteria were clinical, hormonal (FT3, FT4, TSH values), serologic (presence of circulating anti-thyroid-peroxidase antibodies, TPO-Ab, and anti-thyroglobulin antibodies, TG-Ab), and ultrasonographic evidence of AITD or NTG. Patients with suspected AITD by clinical, hormonal or ultrasonographic findings without circulating anti-thyroid antibodies were not included. In the control group, patients having circulating anti-thyroid antibodies were not included. Other exclusion criteria were: (a) presence of known environmental factors capable of triggering the onset of AITD in genetically susceptible individuals such as iodinated drugs (contrast agents, disinfectants, amiodarone), non-iodinated drugs capable to affect thyroid function (lithium, radio iodine therapy, IFN), stress events (mourning, shock, illness) and recent pregnancy (< 6 months); (b) patients with uncertain diagnosis or thyrotoxicosis or positive TSH-receptor antibodies (TSH-R-Ab); (c) patients with certain AITD pre-existing to HCV infection; (d) HCV positive patients treated with IFN.

In all patients serum TSH (normal range: 0.35-2.80 mU/l), FT3 (normal range: 3.8-8.9 pmol/l) and FT4 (normal range: 9-20 pmol/l) were assessed by immunochemiluminiscence. Serum levels of TG-Ab, TPO-Ab and TSH-R-Ab were detected by direct chemiluminescence (ACS:180). All patients, after freely given informed consent, underwent detection of circulating HCV antibodies, HBsAg and anti-HBs antibodies. HCV antibodies were measured using microparticular enzyme immuno-assay (MEYA) (AxSYM HCV version 3, Abbott, Italy): positive titers were considered those with S/CO > 1.00. HBs antibodies were detected by MEYA (AxSYM AUSAB, Abbott, Italy): positive titers were considered those higher than 10,0 mU/ml. HBsAg was measured with MEYA (AxSYM HbsAg V2, Abbott, Italy) considering positive S/CO > 1.00.

Frequencies and descriptive statistics were obtained by computed conventional techniques: the values are presented as mean ± standard deviation (SD). Group differences were analysed using the chi-square test and *t* test, where appropriate. The test was considered statistically significant if $P < 0.05$.

Results

Personal and hormonal data of patients (AITD) and controls (NTG) are shown in Table I. There were no significant differences between the two groups.

In the AITD patients, only TG-Ab were positive in 17/112 (15.1%) patients with AITD, only TPO-Ab were present in 35/112 (31.3%) while both types of antibodies were positive in 60/112 (53.6%) of patients.

HCV antibodies were positive in 13/112 (11.6%) of AITD patients and in 2/88 (2.3%) of NTG controls ($P < 0.05$) (Figure 1). Two/13 (15.3%) of HCV positive patients with AITD had circulating TG-Ab, 5/13 (38.4%) had TPO-Ab and 6/13 (46.1%) had both antibodies. In the AITD group HCV positive showed no significant difference in the prevalence of treated hypothyroidism: 7/13 (53.8%) were under L-thyroxine treatment for hypothyroidism and 69/99 (69.7%) HCV negative patients were treated. HCV positive patients with AITD showed a higher, although not significant, mean age (63.0 ± 11.4 years) than AITD patients HCV negative (47.5 ± 13.6 yrs). A higher prevalence of HCV was found in female patients (F/M = 9/4). Both HCV positive patients of control group were female (age 34 and 68 yrs).

Table I. Clinical and hormonal data of the patients (AITD) and controls (NTG).

Parameter	AITD	NTG
N°	112	88
Age (yrs)	49.8 ± 14.9	50.2 ± 13.5
Sex (F/M ratio)	94/18	73/15
FT3 (pmol/l)	4.5 ± 0.4	4.2 ± 0.4
FT4 (pmol/l)	12.1 ± 3,5	13.4 ± 4.1
TSH (mU/l)	2.1 ± 1.2	1.9 ± 1.2
L-T4 treated (N°) (%)	82 (73.2%)	69 (78.4%)

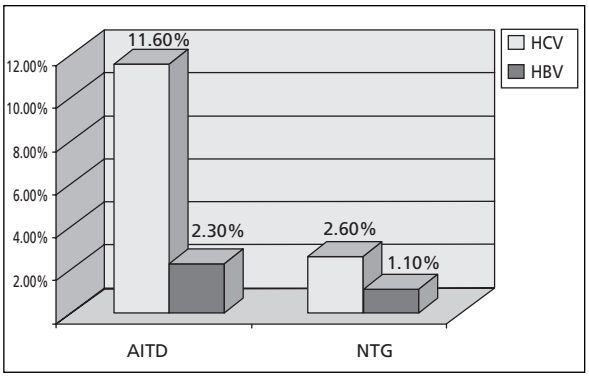

Figure 1. HCV and HBV prevalence in the patients (AITD) and in controls (NTG). $P < 0.05$ between AITD patients with HCV and NTG controls.

HBV antibodies and HBsAg were found in 3/112 (2.6%) of AITD patients and in 1/88 (1.1%) of controls (NTG) (P = NS). None of these AITD patients had only circulating anti-thyroid antibodies; 2 of these patients were positive for only HBs antibodies (vaccinated subjects).

Discussion

The present study shows that the prevalence of HCV antibodies is statistically different ($P < 0.05$) in patients with AITD (11.6%) than in NTG controls (2.3%), in agreement with other studies[11,12], the second group having HCV prevalence similar that of the general population (1.5-2%)[17]. On the other hand, there was no significant difference between AITD patients and NTG controls in the prevalence of HBV antibodies (2.6% versus 1.1% respectively): in both groups it was similar to that of the general population (about 2.5%)[18]. However, other authors were unable to demonstrate a difference in the prevalence of HCV antibodies, evaluating only 28 AITD patients and 23 controls[13]. Similarly, Loviselli et al. surveying the general population of two villages in Sardinia, Italy, found a concordance in HCV antibodies and anti-TPO presence in a small minority of subjects (0.65%)[14].

The strong association between HCV infection and autoimmune thyroid disease suggests that HCV, but not HBV, could be one of the environmental factors responsible for the breakdown of immunological tolerance. Various hypothesis have been proposed about the pathogenetic mechanism[19,20]. One possible explanation is molecular mimicry[21], but other findings suggest that a viral infection capable of inducing an α-IFN response in the host, as HCV, could be involved in the development of AITD in genetically predisposed individuals[7].

Studies carried out in HCV positive patients to investigate the relationship between HCV and AITD are numerous[5,8,22,23]. The prevalence of thyroid antibodies in patients with HCV infection varied markedly, ranging from 2% to 31%. Differences in age, gender and geographical distribution in the populations studied could explain such contradictions. Antonelli et al. investigated the prevalence of thyroid disorders in 630 consecutive patients with HCV and in three control groups and found a prevalence of 17% for TG-Ab and 21% for TPO-Ab in HCV patients, suggesting a link between HCV and AITD[16]. Gane-Carrie et al., who studied 97 HCV and 97 controls, found that the overall prevalence of thyroid disorders was higher in patients than in controls (17% versus 4%) and the prevalence of anti-thyroid antibodies was significantly different between the two groups[8]. Fernandez-Soto et al. reported that 27 of 134 (20%) HCV positive patients had TPO-Ab, as opposed to only two of 41 (5%) HBV positive controls[4]. Only two studies carried out in HCV positive patients showed absence of association with AITD[24,25].

In conclusion, in accordance with most authors, our data clearly demonstrated a strong association between HCV and AITD, in particular in elderly patients. In contrast with the literature reports, our study also showed a high prevalence of HCV in female patients, even if without statistical significance for the small number of patients. In accordance with other reports[4,16,23] no association was found between HBV and autoimmune thyroiditis. HCV, but not HBV, probably inducing an α-IFN response, could be one of the environmental factors involved in the AITD development. These data outline the interest of systematic TPO-Ab and TG-Ab detection in all HCV patients, independently of IFN therapy, and also suggest the utility of HCV screening in all AITD patients.

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