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ORIGINAL ARTICLE

Thyroid involvement in ankylosing spondylitis and relationship of thyroid dysfunction with anti-TNF α treatment

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Abstract Association between rheumatological and autoimmune thyroid disorders has been demonstrated by many studies. However, a few data exist indicating the association between thyroid disorders and ankylosing spondylitis (AS). In this study, the frequency of thyroid disorders in patients with AS and the impact of anti-TNF α therapy on this were investigated. Data of 108 patients (female/male (F/M) 27/81) were analyzed. Data on free T3, free T4, thyroid-stimulating hormone, anti-thyroid peroxidase antibodies (TPO), anti-thyroglobulin antibodies, and thyroid ultrasound were assessed retrospectively. 44 (F/M 15/29) patients were receiving anti-TNF α, while 64 (F/M 12/52) were receiving other drugs [(sulfasalazine, anti-inflammatory drug (NSAIDs)]. Among those not receiving anti-TNF α therapy, TPO level was high in 23 patients (mean TPO value 86.69 ± 65.28 U/ml), while it was high only in nine receiving anti-TNF α (mean TPO 36.61 ± 14.02 U/ml) ($p < 0.05$). Investigating the data regarding gender in both populations, autoimmune thyroid disease frequency was found to be lower in the patient group receiving anti-TNF α treatment. Subclinical hyperthyroidism was discovered in three patients (one female two male), and subclinical hypothyroidism in two (two male). Thyroid nodule was detected in 29 patients. It was concluded that the frequency of thyroid autoimmune disease was higher in our study than that reported in the literature, and the frequency of thyroid disorder in patients with AS was lower in those receiving anti-TNF α compared to those not. This may arise from the role of TNF α on pathogenesis of thyroid disorders.

Keywords Ankylosing spondylitis · Anti-TNF α treatment · Thyroid dysfunction · TNF α

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Introduction

Ankylosing spondylitis is a chronic inflammatory rheumatological disease of the axial skeleton manifested by back pain and progressive stiffness of the spine. Association between rheumatological and autoimmune thyroid disorders has been demonstrated before. Presence of this association has been illustrated by many studies particularly regarding rheumatological disorders having autoimmune etiology such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjogren syndrome (SS), and scleroderma (PSS) [1–5]. Autoimmune etiological possibilities are also being discussed for AS though there are few studies concerning the thyroid status in this inflammatory rheumatic disease [6–8].

Biologic agents targeting TNF α are efficacious in AS. Etanercept, infliximab, and adalimumab (anti-TNF α agents) have been shown in randomized placebo-controlled trials of short duration to significantly reduce disease activity, including pain and stiffness as well as improving function, spinal movement, and quality of life.

Although the effect of anti-TNF α agents on thyroid hormone metabolism is not well known, anti-TNF α

treatment improves thyroid function in hypothyroid patients with RA in Raterman et al. study [9]. In this study, we tried to evaluate the frequency of thyroid disorders in the patient group of ankylosing spondylitis and effect of anti-TNF α treatment on thyroid dysfunction.

Material and method

Files of 260 patients with AS fulfilling modified New York criteria and presenting to rheumatology outpatient clinic between January 2008 and May 2011 were analyzed. A total of 108 patients, 27 female, 81 male (mean age: 34 ± 1.14) whose serologic and ultrasonographic data were available were evaluated.

Thyroid status: Serum fT3 (normal range 2.3–4.2 pg/ml), fT4 (normal range 0.74–1.52 ng/dl), and TSH (normal range 0.35–5.50 uU/ml) levels were measured by microparticle enzyme immune assay (AxSYM; Abbott Diagnostics). TPO and ATg levels were measured by Siemens (Advia Centaur CP) Immunoassay system. Levels over 60 U/ml were considered as positive for autoimmune thyroid disease.

The patients' thyroid statuses were defined as below:

1. Euthyroid; TSH level and free T3 and T4 levels between the normal ranges.
2. Hypothyroid; TSH level over 5.50 uU/ml and fT4 level lower than 0.74 ng/dl.
3. Hyperthyroid; TSH level lower than 0.35 uU/ml and fT4 level over 1.52 ng/dl.

TSH level below 0.35 IU/ml and free T3 and T4 levels between the normal ranges were considered as subclinical hyperthyroidism. TSH levels over 5.5 mIU/ml and free T3 and free T4 levels between the normal ranges were considered as subclinical hypothyroidism.

Thyroid US: Patients who had attended the endocrinology outpatient clinic and were suspected to have thyroid disease were investigated with clinical examination, laboratory and radiological methods. Thyroid US was performed with Logic C3 (GE medical system, Milwaukee, USA) equipped with a linear transducer operating at 8.5–13 mHz. During US examination, following parameters were evaluated carefully: thyroid parenchyma echogenicity, presence of nodule formation, echo structure of nodules (solid, cystic, or mixed), echogenicity (hyper, iso, or hypoechoic), margins of the nodules (well-defined, irregular, blurred), and presence of calcifications in the nodules. After the assessment of sonographic features, US-guided Fine Needle Aspiration (FNA) was performed by an experienced endocrinologist with 23-gauge needles to all the nodules greater than 10 mm and to the nodules that had suspicious imaging. Cytological material was smeared on slides immediately after aspiration (solid lesions) or after cytocentrifugation (in the case of fluid collections) and stained by May-Grunwald-Giemsa and Papanicolaou stains. Cytological specimens were evaluated by an experienced cytopathologist and classified as benign, suspicious, or malignant. Samples were defined as sufficient when six or more clusters of follicular cells with each group containing at least ten follicular cells were present on the slides. Cases with benign cytology had clinical and US control after 6 months to rule out changes in nodule volume or clinical features. In the case of nodule growth, a second US-guided FNA was performed to rule out overlooked malignancies. All patients with suspicious or malignant cytology underwent surgery.

The study was approved by the medical ethics committee.

Statistical analysis

Data were processed on a personal computer using the Statistical Package for Social Sciences software (SPSS, Chicago, İllinois) version 15.0 and statistical significance level was set at 0.05.

Results

In our study, 44 patients were receiving anti-TNF α, while 57 were receiving sulfasalazine and NSAIDs, and seven were receiving only NSAIDs.

The demographic data of the patients has been shown on Table 1. Subclinical hyperthyroidism was discovered in three patients (1 female/2 male) and subclinical hypothyroidism in two (two male) patients. All of these five patients were being treated with sulfasalazine. All the patients were euthyroid in the patient group receiving anti-TNF α treatment; thyroid dysfunction was not registered.

Anti-TPO antibody level was higher than normal in 32 (29 %) patients and ATg in 12 (11 %). Anti-TPO level of 23 patients among those not receiving anti-TNF α therapy was high (mean TPO value 86.69 ± 65.28 U/ml), while that of nine patients among those receiving anti-TNF α was lower (mean TPO 36.61 ± 14.02 U/ml) ($p < 0.05$).

Table 1 Demographic data of the patients

Mean age	34 ± 1.14
Mean disease duration (month)	47.86 ± 4.55
Female/male	27/81
Patients receiving anti-TNF α	44
Patients using sulfasalazine	57
Patients using only NSAID	7

However, there was no difference between those receiving and not receiving anti-TNF α regarding ATg levels ($p > 0.05$).

When the patients were investigated in terms of gender, it was observed that 15 female patients had received anti-TNF α therapy, while 12 female patients had not. Anti-TPO level of 12 patients among those not receiving anti-TNF α therapy was high (mean TPO value 97.50 ± 7.77 U/ml), while that of 15 patients among those receiving anti-TNF α was lower (mean TPO 29.07 ± 4.48 U/ml) ($p < 0.005$). Similar results were discovered in the male population. 29 male patients had received anti-TNF α therapy, while 52 male patients had not. Anti-TPO level of 52 patients among those not receiving anti-TNF α therapy was high (mean TPO value 87.69 ± 9.69 U/ml), while that of 29 patients among those receiving anti-TNF α was lower (mean TPO 40.51 ± 6.65 U/ml) ($p < 0.005$).

Thyroid nodule was discovered in 29 patients, multinodular goiter in nine patients and single nodule in 20 patients. There was no meaningful difference about thyroid nodule frequency between those receiving and not receiving anti-TNF α therapy ($p > 0.05$). FNAB findings of one patient were reported as malignant cytology, and when this patient was operated with his own consent, the result was compatible with papillary microcarcinoma. He was treated with total thyroidectomy and levothyroxin suppressive treatment.

Clinical features of patients receiving and not receiving anti-TNF α treatment has been shown on Table 2.

Discussion

Ankylosing spondylitis that affects the axial and peripheral skeleton has a reported prevalence of 0.2–1.4 % [10]. Symptoms usually begin in the third decade of life and the male/female ratio is 2–3:1. NSAIDs are the first choice in the treatment of AS. The efficacy of biologic therapy is relatively more important in the management of AS. TNF α is the most important cytokine in the pathogenesis of AS. Evidence for the role of TNF α in the pathogenesis of AS includes biopsy specimens from sacroiliac joints and entheses in AS patients showing increased concentrations of TNF Messenger RNA [11]. Although the effect of anti-TNF α treatment on thyroid dysfunction is not known precisely, Allanore et al. [12] described a 37-year-old woman who developed transient hyperthyroidism while being treated with anti-TNF α (etanercept) for active RA, and van Lieshout et al. [13] described a 70-year-old woman who developed Graves' disease while being treated with anti-TNF α (Adalimumab) for active RA. But Chen et al. investigated the effect of TNF α in experimental granulomatous autoimmune thyroiditis in their study by giving anti-TNF α treatment at days 19–21 and 48. They found that the thyroid lesions had regressed at day 48 with anti-TNF α treatment. With this finding, they concluded that anti-TNF α treatment was suppressing inflammation and fibrosis by regulating apoptosis and proinflammatory cytokine secretion [14]. In another study, the patients with RA were treated with adalimumab for 6 months, and it was discovered that anti-TNF α treatment had ameliorated the thyroid dysfunction in hypothyroid patients [9]. In the case report of Sabugo et al. [15], thyroid hormone replacement dose decreased with anti-TNF α treatment in a patient who had symptoms of acne, synovitis, hyperostosis, pustulosis (SAPHO syndrome), and hypothyroidism. In another case report, severe hypothyroidism was observed after TNF α treatment prescribed for cutaneous T-cell lymphoma [16]. According to the results of our study, autoimmune thyroid disease was discovered less frequently in the patient group receiving anti-TNF α treatment.

Autoimmune thyroid disease (Hashimoto's thyroiditis) is 15–20 times as frequent in women as in men. It occurs especially during the decades from 30 to 50, but may be seen in any age group, including children [17]. In our patient group, mean age was similar to the population, but the disease was diagnosed more frequently in male population because ankylosing spondylitis is more frequently observed in males. It is certain that it exists with a much higher frequency than is diagnosed clinically, and its frequency seems to be increasing. Family studies always bring to light a number of relatives with moderate enlargement of

Table 2 Clinical features of patients receiving and not receiving anti-TNF α treatment

	Patients receiving anti-TNF α therapy (total *n*: 44)	Patients not receiving anti-TNF α therapy (total *n*: 64)
Female/male (F/M)	15/29	12/52
F/M subclinical hyperthyroidism	0/0	½
F/M subclinical hypothyroidism	0/0	0/2
F/M patients with high anti-TPO	3/6	9/14
F/M mean TPO value	29.07 ± 4.48/40.51 ± 6.65	97.50 ± 7.77/87.69 ± 9.69
F/M patients with high anti-ATg	2/3	2/5
F/M thyroid nodule	5/9	6/9

the thyroid gland suggestive of Hashimoto's thyroiditis. Many of these people have ATg and TPO antibodies, and most are entirely asymptomatic. In addition to overt thyroiditis, roughly 10 % of most populations have positive ATg and TPO antibody test results [17, 18] in the apparent absence of thyroid disease by physical examination. In a classic study of an entire community, Tunbridge et al. [17] found that 1.9–2.7 % of women had present or past thyrotoxicosis, 1.9 % had overt hypothyroidism, 7.5 % had elevated TSH levels, 10.3 % had test results positive for TPO (microsomal antigen) Ab measured by hemagglutination assay (MCHA), and about 15.0 % had goiter. Men had 10- to 4-fold lower incidences of thyroid abnormalities. In our patient group, subclinical hyperthyroidism was discovered in three patients (1 female/2 male) 2.77 %, and subclinical hypothyroidism in two (two male) patients 1.85 %. Besides, Anti-TPO antibody level was found to be higher than normal in 32 patients (29 %) and ATg in 12 patients (11 %). Women with both positive antibody test results and raised TSH levels become hypothyroid at the rate of 5 %/year [19]. A reasonable approximation of the prevalence of positive antibody tests in women is greater than 10 %, and of clinical disease is at least 2 %. Men have one-tenth of this prevalence. None of our patients had overt hypothyroidism, but there was only subclinical thyroid dysfunction in the laboratory data of patients not receiving anti-TNF α treatment, predominantly in the male patients. Anti-TPO antibody levels were also higher in the patient group of not receiving anti-TNF α treatment**.** When the data were investigated regarding gender, in both female and male populations, autoimmune thyroid disease frequency was found to be lower in the patient group receiving anti-TNF α treatment. There was no gender difference regarding the effect of anti-TNF α treatment. This can be explained by the effects of anti-TNF α treatment on thyroid function.

By the least sensitive method which is palpation, 5 % of people are found to have nodules. However, with the increased utilization of US for the evaluation of nonthyroid lesions of the neck, incidental finding of unsuspected thyroid nodules has increased, with some studies reporting a prevalence of up to 50 % in individuals over the age of 50 years. Thyroid nodules are very common in clinical practice, and although most are benign, approximately 5 % of people are found to have nodules [20]. In our study, 26.85 % of the study population had thyroid nodules and FNA was performed in all nodules, which were over 10 mm and looked suspicious by ultrasound. Only one patient was diagnosed as suspicious by FNA, and after the thyroidectomy, specimen was diagnosed as papillary thyroid microcarcinoma. This patient is being treated with levothyroxin suppressive treatment.

In the study that was performed by Bianchi et al. [7] only ankylosing spondylitis was not associated with any functional abnormality or autoimmune phenomena in the thyroid, but patients with RA and psoriatic arthritis had higher than normal FT4 levels and increased prevalence of anti-TPO. However, in our patient group consisting of 108 patients, autoimmune thyroid disease was observed more frequently than normal population. Lange et al. [8] had established a relationship between low T3 syndrome and acute inflammatory activity of AS in female AS patients, but in our study, low T3 levels was not observed in the laboratory data of our patients.

The drawback of our study is the collection of the data retrospectively. It could be interpreted better if the presence of thyroid dysfunction could have been demonstrated before and after anti-TNF α treatment, and the impact of anti-TNF α treatment on thyroid function could be shown more precisely.

As a result, it can be concluded that the frequency of thyroid autoimmune disease has been greater than that in the literature; however, in the patient group receiving anti-TNF α treatment, thyroid dysfunction has been observed less frequently both in the female and male groups. This finding may be the result of the role of TNF α in the pathogenesis of thyroid disease. More controlled studies are required to demonstrate these findings.

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