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Thyroid Function Tests in Ankylosing Spondylitis Patients on Anti-Tumour Necrosis Factor Treatment

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Introduction: Ankylosing spondylitis (AS) is a chronic inflammatory disease. Thyroid dysfunctions are more frequent in patients with inflammatory diseases. In this study, we aimed to evaluate thyroid functions and thyroid autoantibodies in ankylosing spondylitis patients, to determine the effect of anti-tumor necrosis factor treatment in AS patients and the relationship between thyroid function and autoantibody levels, inflammatory markers and disease activity in ankylosing spondylitis patients.

Materials and Methods: 74 ankylosing spondylitis patients diagnosed according to 1984 Modified New York criteria and Assessment in Spondylarthritis International Society classification criteria were included. 41 of them were receiving anti-tumor necrosis factor treatment and 33 of them were receiving nonsteroid anti-inflammatory drugs. We recorded patients' age, gender, erythrocyte sedimentation rates, C-reactive protein values, blood count, biochemical analysis, thyroid function tests, autoantibody levels, Bath Ankylosing Spondylitis Disease Activity Index.

Results: Mean anti-thyroid peroxidase levels were significant at a high level in ankylosing spondylitis patients receiving anti-tumour necrosis factor compared to patients receiving nonsteroid anti-inflammatory drugs (p= 0.009).Negative correlation was found between thyrotropin-stimulating hormone and C-reactive protein(r=-0,264, p=0,023).A positive correlation was found between free thyroxine and C-reactive protein (r=0,436,p=0,009), anti-thyroid peroxidase positivity and erythrocyte sedimentation rate (r=0,384,p=0,001),anti-thyroglobulin positivity and erythrocyte sedimentation rates and C-reactive protein(r=0,329,r=0,265,p=0,004,p=0,022).

Conclusion: The frequency of thyroid disorder in patients with AS receiving anti-TNF α was lower compared to patients receiving nonsteroid anti-inflammatory drugs. We can consider that anti-TNF α treatment could reduce autoimmune thyroid diseases and had a positive effect on thyroid functions.

Keywords: Thyroid function, ankylosing spondylitis, anti-tumour necrosis factor treatment

Introduction

Ankylosing spondylitis (AS) is a chronic, systemic, autoimmune, inflammatory disease that characteristically affects the sacroiliac joints and spinal column (1). The diagnosis of AS is based on the Modified New York criteria (mNY) and Assessment in International Spondyl-arthritis Society (ASAS) classification criteria (2-3). The systemic lupus erythematosus (SLE) (4), vasculitis (5), interstitial lung disease (6), sarcoidosis (7), multiple sclerosis (8) and auto

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immune liver diseases (9) have been reported as concomitant autoimmune diseases with AS. This has been explained by genome-wide association studies. In these studies, numerous risk loci have been defined for these auto immune disorders (10). Thyroid dysfunctions are also frequent in rheumatic disease patients (11). These diseases are rheumatoid arthritis (RA) (12), SLE (13), Sjogren's syndrome (SS) (14) and AS (15). Lazúrová et al. (12) defined the prevalence of autoimmune thyroid disease (AITD) and anti-thyroid autoantibodies in RA patients. They reviewed the role of genetics in the association of both AITD and RA. Appenzeller et al. (13) reported the association between thyroid dysfunction and SLE. Sun et al. (14) performed a systematic review to demonstrate the risk of thyroid disease in SS patients. They suggested that SS patients should be screened for thyroid disease. Lange et al. (15) investigated thyroid autoimmunity. As a result of their study, the prevalence of anti-thyroid antibody was significantly higher in AS.

In our study, we aimed to evaluate thyroid function tests (TFTs) and autoantibodies, to determine the effect of anti-tumor necrosis factor (TNF) treatment in AS patients and the relationship between thyroid function and autoantibody levels, inflammatory markers and disease activity in AS patients. To the authors' knowledge, this is the first study that evaluated disease activity in AS patients with TFTs and autoantibodies.

Materials and Methods

Ethical Statement

This study was approved by the ethics committee and carried out from July 2016 to December 2016. All participants signed the informed consent form (Approval: 2017-1046).

74 AS diagnosed according to 1984 mNY and ASAS classification criteria were included (2-3). mNY criteria are as following; having at least 1 clinical criterion (inflammatory back pain, limitation of mobility of the lumbar spine, or limitation of chest expansion) plus radiologic criteria (radiographic sacroiliitis; grade 2 bilateral or grade 3-4 unilateral sacroiliitis) (2). According to ASAS criteria AS diagnosis is possible either by using the 'imaging' arm with signs of active sacroiliitis in magnetic resonance imaging (MRI) with at least one other spondylarthritis (SpA)feature or by using the 'clinical' arm, where the presence of human leukocyte antigen-B27 (HLA-B27) is mandatory with an additional two or more SpA features (3). 41 of AS patients were receiving anti-TNF treatment and 33 of them were receiving non-steroid anti-inflammatory drugs (NSAIDs). Braun et al. stated the conditions for treatment with anti-TNF therapy should be the diagnosis of AS (usually by the mNY criteria), active disease (BASDAI>4 and expert opinion) for at least 4 weeks, failure of NSAIDs for a minimum 3-month trial, failure of intra-articular steroids (if indicated) and failure of sulfasalazine (if predominant peripheral arthritis) (16). All participants had data about thyroid hormones and autoantibody levels.

Inclusion criteria were patients who were over 18 years and diagnosed with AS according to Modified NY criteria. Exclusion criteria were (1) pregnancy, lactation; (2) previous thyroid diseases; (3) presence of additional co-morbidity (diabetes mellitus, asthma, chronic obstructive pulmonary or hepatic-renal-vascular cardiac disease, etc.); (4) use of drugs which may cause thyroid diseases. All the patients' age, gender, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) value, TFTs (thyroid

stimulating hormone (TSH), thyrotropin (FT_3), thyroxine (FT_4), auto antibody (anti-thyroid peroxidase (anti-TPO), anti-thyro globulin (anti-TG) and BASDAI scores were recorded.

Ankylosing Spondylitis disease activity was defined according to the BASDAI score. Based on this score, BASDAI<4.0 was defined as low disease activity and BASDAI>4.0 as high disease activity. It includes six items questioning the patient's fatigue, the severity of the neck, back and hip pain, the severity of peripheral joint pain, tenderness on pressure and palpation, and severity of morning stiffness (17). BASDAI scores and laboratory features were recorded in the 3rd month of treatment.

Erythrocyte sedimentation rate' (ESR) normal range was defined as 0-20 mm/h, CRP' as 0-5 mg/L, respectively (18-19). TSH' normal range was defined as 0.35-4.94 uU/ml, FT_3' normal range was as 1.71-3.71 pg/ml, FT_4' normal range was defined as 0.70-1.48 ng/dl, respectively (20). We defined the thyroid status as Euthyroid: TSH, FT_3 and FT_4 levels between the normal ranges, hypothyroid: TSH level over 4.94 uU/ml and FT_4 level lower than 0.70 ng/dl, hyper thyroid: TSH level lower than 0.35 uU/ml and FT_4 level over 1.48 ng/dl (21). Subclinical hyper thyroidism was defined as a TSH level below 0.35 uU/ml with FT_3 and FT_4 levels between the normal ranges. Subclinical hypothyroidism was defined as TSH levels over 4.94 uU/ml with FT_3 and FT_4 levels between the normal ranges (21). Autoimmune thyroid disease was defined as Anti-TPO levels over 5.61 IU/ml and anti-TG levels over 4.11 IU/ml (21).

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) v19. Normally distributed variables were tested with independent T-test, non-normally distributed variables were tested with Mann-Whitney U test. Descriptive was given as mean± standard deviation (SD) and median (25-75 percentiles). $p<0.05$ was considered statistically significant.

Results

The mean age was 42.7±8.6 years in AS patients. There were 31 male, 10 females AS receiving anti-TNF α. The mean age was 41.8± 10.2 years in the NSAIDs group. There were 23 males, 10 females in the NSAIDs. There was no statistically significant difference between groups in terms of demographic features (age and sex), ESR, CRP, complete blood count (CBC), biochemical analysis, TFTs and anti-TG levels ($p>0.05$). Mean anti-TPO levels were significant at a high level in the AS patients receiving anti-TNF α compared to the NSAIDs group ($p=0.009$). Demographic and laboratory features of patients are presented in Table 1.

Table 1. Demographic and laboratory features of the patients with AS

Variables	Anti-TNFα group (n:41)	NSAIDs group (n:33)	p
Age (years)	42.7±8.6	41.8±10.2	
Gender ▪ Male (n) ▪ Female (n)	 31 10	 23 10	
ESR (mm/h)	22 (13.5-30.5)	18 (9-33)	0.267
CRP (mg/L)	7.5 (2.7 -17)	5.3 (1.8 -12.5)	0.504
Thyroid function tests ▪ FT_3 (pg/ml) ▪ FT_4 (ng/dl) ▪ TSH (μU/ml)	 3±0.5 1±0.1 1.1±0.6	 3.1±0.5 1±0.1 1.3±0.7	 0.35 0.485 0.37
Anti-TPO	0.27 (0.18-0.55)	0.11 (0-0.5)	0.009
Anti-TG	1.57 (0.99-2.49)	1.43 (0.92-2.49)	0.556

SD: Standard deviation; ESR: Erythrocyte sedimentation rates; CRP: C-reactive protein; FT_3: Free triiodo thyronine; FT_4: Free thyroxine; TSH: thyroid stimulating hormone; Anti-TPO: Anti-thyroid peroxidase; Anti-TG: Anti thyroglobulin.

A negative correlation was found between TSH and CRP (r=-0,264, p=0,023). A positive correlation was found between FT4 and CRP (r=0,436, p=0,009), anti-TPO positivity and ESR (r=0,384; p=0,001), anti-TG positivity and ESR and CRP (r=0,329; r=0,265; p=0,004; p=0,022) (Table 2).

Table 2. Correlations between Bath AS Disease Activity Index, ESR and CRP levels with values related to thyroid of the patient

Variables	BASDAI	ESR (mm/h)	CRP (mg/L)
FT_3 (pg/ml)			
▪ r	-0,066	-0,209	-0,158
▪ p	0,579	0,073	0,179
FT_4 (ng/dl)			
▪ r	-0,056	0,228	0,436
▪ p	0,636	0.051	0,009
TSH (μU/ml)			
▪ r	0,252	0,133	-0,264
▪ p	0,031	0,260	0,023
Anti-TPO positivity			
▪ r	0,134	0,384	0,153
▪ p	0,256	0,001	0,192
Anti-TG positivity			
▪ r	-0,042	0,329	0,265
▪ p	0,720	0,004	0,022

FT_3: Free triiodo thyronine; FT_4: Free thyroxine; TSH: thyroid stimulating hormone; Anti-TPO: Anti-thyroid peroxidase; Anti-TG: Anti-thyroglobulin; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ESR: erythrocyte sedimentation rates; CRP: C-reactive protein

Discussion

Thyroid disorders which are seen during anti-TNF α treatment can be coincidence or a paradoxical event and at the same time, they may be a marker of immunogenicity (22). The effect of anti-TNF α treatment on thyroid functions is not well known yet.

The study of Lange et al. included 22 AS patients and 22 controls (10). They investigated FT_3, FT_4, total triiodothyronine (TT_3) levels, and anti-thyroid antibodies. As a result of their study, the prevalence of anti-thyroid antibodies was significantly higher in AS patients. Peluso et al. (23) evaluated TFTs and antithyroid anti bodies in 357 spondylarthritis SpA and 318 controls. They announced that thyroid auto immunity was significantly higher in SpA. Acay et al. (24) evaluated TFTs, anti-thyroid anti-bodies in 122 controls, and well-defined 201 patient (including AS). FT_4, TSH, and anti-thyroid antibodies were higher in well-defined patients. Subclinical hypothyroidism was found in 3 patients. The study by Emmungil et al (25) investigated TFTs levels and anti-thyroid antibody positivity in 80 AS patients, 62 Sjögren syndrome (SjS) patients, and 80 healthy controls. The positivity of at least one of thyroid antibodies was significantly more frequent in AS patients (p=0.017). Tarhan et al. (26) studied TFTs and anti-thyroid antibodies. Their study included 44 AS patients receiving anti-TNF α and 64 patients receiving other drugs. As a result of the study anti-TPO level was higher in 23 patients receiving other drugs ($p<0.05$). They announced that autoimmune thyroid disease was lower in patients receiving anti-TNF α.

Tumour necrosis factor α (TNF α) and TNF α receptors have been found in human thyroid tissue (27). This can explain why autoimmune thyroid disorders are seen during anti-TNF α treatment (23). And the frequency of thyroid disorders which are seen during anti-TNF α treatment could be explained by this common pathology.

In our study, we aimed to evaluate TFTs and autoantibodies in AS patients receiving anti-TNF α and NSAIDs. As a result, we found higher anti-TPO levels in AS patients receiving anti-TNF α. Also, we found a negative correlation between TSH and CRP values, while a positive correlation between FT_4 and CRP, anti-TPO positivity and ESR, anti-TG positivity and ESR,

and CRP. The frequency of thyroid disorder in patients with AS receiving anti-TNF α was lower compared to the NSAIDs group. As a result of our study, anti-TNF α treatment could reduce autoimmune thyroid diseases and had a positive effect on thyroid functions. We can consider that when AT disease developed in AS patients receiving anti-TNF α, this treatment could improve thyroid disease. ATPO and ATG

The study has some limitations. The general ability of our findings is limited because of the relatively small sample size. Also, we have not data about anti-TPO and anti-TG values at baseline and at a time after treatment. There is a need for further research with larger samples and long-term follow-up to replicate the findings of this study.

Conclusion

According to our study, we can consider that FT_4, anti-TPO and anti-TG values can be used as inflammatory markers in AS patients. However, we believe that more studies are needed for this research.

Conflict of Interest

The authors have declared no conflict of interest for the present article.

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