ROSACEA IS ASSOCIATED WITH THYROID AUTOIMMUNITY: A CASE CONTROL STUDY

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Abstract

Background and aims. There are numerous intrinsic and extrinsic factors associated with the pathophysiology of rosacea, including immune dysregulation. The aim of this study is to determine the relationship between rosacea and thyroid autoimmunity.

Methods. Seventy-two patients with rosacea and 62 rosacea-free control subjects were included in the study. Serum free triiodothyronine (fT3), free thyroxine (fT4), thyrotropin releasing hormone (TSH), antithyroid peroxidase antibody (ATPO), antithyroglobulin (anti-Tg), prolactin, dehydroepiandrosterone sulfate (DHEAS), basal cortisol, serum CRP concentrations and erythrocyte sedimentation rate were measured.

Results. The number of the cases with high levels of CRP, anti-M and prolactin in rosacea group were significantly higher than the controls ($p < 0.05$), there was no significant difference according to other parameters in both groups ($p > 0.05$). There was no significant difference according to the presence of a thyroid disease in both groups ($p > 0.05$). The decrease in the CRP parameter in patients with the disease duration of 1-5 years was found to be statistically significant ($\beta_{\text{CRP}} = -0.251$, $p_{\text{CRP}} < 0.05$). There was no statistically significant difference according to disease severity or disease duration ($p > 0.05$).

Conclusions. Rosacea may be associated with high thyroid autoantibodies, prolactin and CRP levels, in which immune-endocrine interactions are important.

Key words: rosacea, autoimmunity, thyroid, antimicrobial antibody, antithyroglobulin antibody, prolactin, dihydroepiandrosterone sulfate.

INTRODUCTION

Rosacea is a common skin disorder characterized by symmetric facial erythema, stinging sensation, inflammatory papules and pustules and telangiectasias. It is more common in women and individuals with skin type I and III (Fitzpatrick phenotypes) (1). The exact cause and pathogenesis of rosacea is still unknown. However, several potential etiologic agents and

processes, which include vascular reactions, chronic inflammatory responses, emotional stress, environmental triggers, UV irradiation, foods and chemicals ingested, microorganisms and Demodex mites, either alone or in combination may be responsible in the pathogenesis of rosacea (2-4).

Dysregulation of the innate immune system may be important in promoting the clinical features of rosacea (5, 6). Demodex folliculorum and dermal infiltrates with a predominance of CD4+ T-helper (TH) cells over CD8+ T cells in pathologic sections support that cell-mediated immune responses have an important role in the pathogenesis of rosacea (7). Although autoimmunity may also play a role in the pathogenesis of rosacea, but there are conflicting results in the literature (8-10). Some risk loci pointing autoimmunity have been identified in the patients with rosacea. Some rosacea patients may have type 1 diabetes mellitus, celiac disease, multiple sclerosis, and rheumatoid arthritis (10).

Associations between autoimmune thyroid diseases and dermatologic diseases have been reported (11-13). However, there are some conflicting studies about thyroid diseases and rosacea. The aim of this study was to determine the relationship between rosacea and thyroid autoimmunity.

MATERIALS AND METHODS

Study design

The study was a prospective, single-center case-control study of 72 patients with rosacea and 62 rosacea-free control subjects. The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki, and was approved by Cumhuriyet University School of Medicine Human Ethical Committee. Written informed consent was obtained from all patients. Eligible patients (aged ≥ 18 years) with a diagnosis of rosacea were free of systemic comorbidities, including diabetes mellitus, hypertension, coronary disease, and previously diagnosed thyroid

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disease. Rosacea-free control subjects been diagnosed as dermatophytosis were included in the study. All subjects were recruited from the Dermatology clinic at Cumhuriyet University School of Medicine.

Standard criteria developed by the Expert Committee on the Classification and Staging of Rosacea were used for the diagnosis of rosacea. The disease severity was assessed according to the following parameters: erythema (transient and non-transient), telangiectasia, burning or stinging, plaques, dry appearance, edema, and a global assessment of subtypes by both the physician and the patient.

Scores of 0-3 (0, absent; 1, mild; 2, moderate; 3, severe) were assigned to each category, and patients were divided into mild (range, 0-9), moderate (10-18), and severe (19-27) groups (14, 15).

Data, including medical history, information on demographics, smoking and alcohol use were recorded.

Biochemical measurements

Blood samples were drawn from subjects in the morning between 07:30 and 09:00, after an overnight fast. A chemiluminescence immunoassay (Roche Cobas e-601, Indianapolis, USA) was used to determine serum free triiodothyronine (fT3) and free thyroxine (fT4), thyrotropin releasing-hormone (TSH), antithyroidperoxidase antibody (ATPO), antithyroglobulin (anti-Tg), prolactin, dehydroepiandrosterone sulfate (DHEAS), and basal cortisol levels and concentrations. Serum CRP concentrations were determined by nephelometry (Beckman Coulter, Image, USA). ESRs were determined by the Sista ESR 100 (Ankara, Turkey) system based on the modified Westergren sedimentation technique.

The normal reference range for ATPO was 0-5.61 IU/mL, for anti-Tg was 0-4.11 IU/mL, for TSH

was 0.35-4.94 μ IU/mL, for fT4 was 0.7-1.48 ng/dL, for fT3 was 1.71-3.71 ng/dL, for DHEAS was 80-560 μ g/dL, for prolactin was 2.5-17 ng/mL, for CRP was 0-8 mg/L, for cortisol was 5-25 μ g/dL, for ESR was 0-15 mm/h for males and 0-20 mm/h for females. The presence of high TSH, low fT3 and fT4 and high antiTg antibodies was accepted as an autoimmune thyroiditis.

Statistical analysis

All statistical analyses were performed using Statistical Package for Social Sciences (SPSSVersion 22). Data analyses methods included a Mann-Whitney U test, chi-square test, Spearman correlation analysis, and multinomial regression analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

The case group consisted of 56 female and 16 male patients. The control group consisted of 40 female and 22 male subjects. The mean ages in the patient and control groups were 41.2 years (SD=13.2) and 39.5 years (SD=14.1), respectively. There were no statistically significant differences between the groups in terms of age and gender ($p>0.05$).

Although the number of cases with high levels of CRP, anti-M, and prolactin was significantly higher in the patient group than the control group ($p<0.05$), there were no significant differences between the groups in terms of other parameters ($p>0.05$). There was also no significant difference between the groups regarding the presence of a thyroid disease ($p>0.05$) (Table 1). Table 2 shows the correlations between antibodies and hormones in the patient group.

A multinomial logistic regression analysis was performed using age, anti-M, anti-Tg, TSH, fT3,

Table 1. The values of antimicrosomal antibody, antithyroglobulin antibody, prolactin and CRP in both groups

Study groups	Anti-M (IU/mL)		Anti-Tg (IU/mL)		Prolactin (ng/mL)		CRP (mg/L)	
	Normal	High	Normal	High	Normal	High	Normal	High
Rosacea	49	23	47	25	52	20	58	14
Control	53	9	48	14	57	5	59	3
p	0.02		0.13		0.00		0.01	

Table 2. The relationship between autoimmunity and hormones in rosacea group

	Basal cortisol		Prolactin		DHEAS		Anti-M		Anti-TG	
	r*	p	r*	p	r*	p	r*	p	r*	p
Basal cortisol	1.00	-	0.32	0.00	0.29	0.01	-0.30	0.01	-0.22	0.05
Prolactin	0.32	0.00	1.00	-	0.22	0.06	-0.06	0.59	0.03	0.75
DHEAS	0.29	0.01	0.22	0.06	1.00	-	-0.013	0.29	-0.05	0.69
Anti-M	-0.30	0.01	-0.06	0.59	-0.13	0.29	1.00	-	0.54	0.00
Anti-Tg	-0.22	0.05	0.03	0.75	-0.05	0.69	0.54	0.00	1.00	-

*Spearman rho.

fT4, DHEAS, prolactin, CRP, ESR, and basal cortisol parameters according to disease severity. First, a collinearity analysis of these parameters was performed and age, TSH, anti-Tg, CRP, and ESR levels were included in the statistical analysis model. A group of mild rosacea cases was selected as the reference group and analyses were evaluated according to the parameters of the patients in this group. The Cox and Snell R² was determined to be 0.551. No statistically significant parameter was found in the moderate and severe cases of rosacea in the parameter estimation table ($p>0.05$).

A multinomial logistic regression analysis was also performed using age, anti-T, TSH, fT4, fT3, DHEAS, prolactin, CRP, ESR, and basal cortisol parameters according to disease duration (< 1 year, 2-5 years, 6-10 years and >10 years). A collinearity analysis of these parameters was performed and age, fT3, anti-Tg, CRP and ESR levels were included in the statistical analysis model. A group of patients with a disease duration shorter than one year was selected as the reference group and the analyses were evaluated according to the parameters of the patients in this group. The Cox and Snell R² was determined to be 0.586. No statistically significant parameter was found in the parameter estimation table in patients with disease durations of 5- 10 years or longer than 10 years ($p>0.05$). However, the decrease in the CRP parameter in patients with the disease duration of 1-5 years was found to be statistically significant ($\beta_{\text{CRP}} = -0.251$, $p_{\text{CRP}} < 0.05$).

DISCUSSION

Factors such as vascular hyperreactivity, genetic predisposition, innate and acquired immune reactions, and colonization with microorganisms such as *Demodex folliculorum* and *Helicobacter pylori* have been implicated in the pathogenesis of rosacea (16). Among these, abnormalities in the innate immune systems of rosacea patients have been primarily implicated. These abnormalities can increase the skin's susceptibility to the external environment, a potentially influential factor in initiating or aggravating rosacea. Additionally, adaptive immunity in rosacea might contribute to further inflammatory responses (17). Furthermore, CD20+ B cells constitute 10-20% of inflammatory cells in rosacea, and infiltration with plasma cells as well as antibodies have been observed in rosacea. Elevated antinuclear antibody titers are frequent and important findings in rosacea patients. B cell responses reveal the importance of further research in this regard (10).

In our study, we found that anti-M, prolactin, and CRP levels were higher in rosacea patients than in rosacea-free control subjects. However, there was no relationship found between high levels of anti-M and prolactin and disease severity or duration. Prolactin (PRL) is a 23-kDa polypeptide hormone with pleomorphic effects. A variety of tissues in the human body, including the anterior pituitary gland and B and T cells, produce PRL. PRL facilitates the breakdown of immune tolerance by promoting the survival, maturation, and activation of autoreactive B and T cells, dendritic cells, and macrophages (18). Hyperprolactinemia has also been observed to contribute to the break of B cell tolerance, enhance the maturation of B cells, and increase levels of circulating autoantibodies and immunoglobulin deposition. Human B cells increase PRLR expression and PRL secretion following stimulation. The correlation between circulating PRL level and B and plasma cells in the patients with systemic lupus erythematosus (SLE) has been studied, though data on the association between PRL level and disease activity are inconsistent (19, 20). In our study, we found no significant correlation between anti-M antibodies and prolactin levels. Additionally, no significant relationship between PRL levels and disease activity or severity in rosacea patients was found.

One hormone important in the regulation of the immune system is DHEAS. DHEAS levels decrease in chronic inflammatory diseases, including rheumatoid arthritis, SLE, primary Sjögren's syndrome, and polymyalgia rheumatica. DHEAS is a multifunctional adrenal hormone with immunomodulating properties (21). In our study, there was no statistically significant difference between DHEAS levels of the patients and healthy controls. Additionally, there was no observed relationship between DHEAS levels and disease duration in the rosacea patient group. This result suggests that the cellular immune response in rosacea pathogenesis is not promoted by DHEAS.

Both female gender and increasing age have been associated with a higher frequency of thyroid antibody positivity (22), as well as increasing DHEAS and sometimes, refractory acne (23). In our study group, the antibody levels, including anti-M and anti-Tg levels, were not affected by gender and age.

Data on basal cortisol levels in chronic diseases in the literature are controversial (24, 25). According to our results, although there is no observed relationship between basal cortisol levels and disease duration or disease severity, it is important to note that in rosacea patients, ATPO antibody levels are elevated when basal cortisol levels are low. Topical steroids could decrease

basal cortisol levels and induce facial rosaceiform dermatitis (28).

In chronic diseases, thyroid hormones may be altered even without thyroid diseases. Several studies have shown that these alterations also occur in acute diseases and are associated with cytokine activation (27). In our study, there was no statistically significant difference between thyroid hormone levels of patients and healthy controls. There was no observed relationship between TSH levels and disease duration or disease severity.

There are a few limitations in our study. The most obvious limitation was that of a relatively small sample size, preventing the generalization of the findings in rosacea patients. The second limitation was the lack of laboratory analysis of antibodies evaluating autoimmunity, including antinuclear antibodies and rheumatoid factor. The third limitation was that we did not determine ACTH-stimulated cortisol levels.

In conclusion, rosacea may be accepted as a disease that interacts with autoimmune thyroid antibodies and in which immune-endocrine interactions are important.

Conflict of interest

The authors declare that they have no conflict of interest.

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