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Prevalence of Autoimmune Thyroiditis and Other Autoimmune Diseases in Relation to Serum BAFF/APRIL Levels in Prolactinoma Patients

Prolaktinoma Hastalarında Serum BAFF/APRIL Düzeyleriyle İlişkili Olarak Otoimmün Tiroidit ve Diğer Otoimmün Hastalıkların Prevalansı

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ABSTRACT

Objective: There may be an association between hyperprolactinemia and autoimmune diseases, possibly because of the immunostimulatory effect of prolactin. The aim of this study was to investigate the prevalence of thyroid and non-thyroid autoimmune diseases, serum B-cell activating factor (BAFF), and proliferation- inducing ligand (APRIL) levels as indicators of increased autoimmunity, quality of life, depression, and anxiety in patients with prolactinoma.

Methods: Fifty-six premenopausal women with prolactinoma and 50 healthy premenopausal women were included in the study. Autoimmune markers, including anti-nuclear antibody, rheumatoid factor immunoglobulin M (IgM) (RF-IgM), anti-double-stranded DNA (anti-dsDNA), anti-transglutaminase IgA (anti TG-IgA), and anti-Sjogren's syndrome A (anti-ssA), serum BAFF, APRIL and vitamin B12 levels, thyroid function tests, anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin and thyroid Doppler ultrasound, were evaluated. Short-form 36, Beck Depression Inventory, and Beck Anxiety Inventory tests were also used.

Results: The prevalence of autoimmune thyroiditis (AIT) was 32.1% in the patient group, whereas the prevalence of newly diagnosed AIT was similar to controls (p>0.05). Vitamin B12 deficiency was higher in patients with prolactinoma than in controls (25.6% and 9.1%, p=0.016). Autoantibody positivity was found to be similar between the groups (35.7% and 28.1%, p=0.25). Serum BAFF and APRIL levels were not different in patients with prolactinoma than in controls (p>0.05). Quality of life, anxiety, and depression scores were not different between patients with or without AIT and those with or without positivity for any autoantibody (p>0.05).

Conclusion: One-third of the patients were diagnosed with AIT and one-fourth of the patients had vitamin B12 deficiency in our study. However, non-thyroid autoimmune diseases did not increase and no alterations were detected in serum BAFF/APRIL levels in patients with prolactinoma.

Keywords: Prolactinoma, autoimmune thyroiditis, vitamin B12, BAFF, APRIL, quality of life, anxiety, depression

ÖZ

Amaç: Prolaktinin immün sistemi uyarıcı etkisi nedeniyle hiperprolaktinemi ile otoimmün hastalıklar arasında bir ilişki olabilir. Bu çalışmanın amacı tiroid ve tiroid dışı otoimmün hastalıkların prevalansını, artmış otoimmünite, yaşam kalitesi, depresyon, ve prolaktinomalı hastalarda anksiyetedir.

Yöntemler: Çalışmaya prolaktinomalı 56 premenopozal kadın ve 50 sağlıklı premenopozal kadın dahil edildi. Anti-nükleer antikor, romatoid faktör immünoglobulin M (IgM) (RF-IgM), anti-çift sarmallı DNA (anti-dsDNA), anti-transglutaminaz IgA (anti TG-IgA) ve anti-Sjogren sendromunu içeren otoimmün belirteçler A (anti-ssA), serum BAFF, APRIL ve B12 vitamini düzeyleri, tiroid fonksiyon testleri, anti-tiroid peroksidaz (anti-TPO), anti-tiroglobulin ve tiroid Doppler ultrasonu değerlendirildi. Kısa form 36, Beck Depresyon Envanteri ve Beck Anksiyete Envanteri testleri de kullanıldı.

Bulgular: Hasta grubunda otoimmün tiroidit (AIT) prevalansı %32,1 iken, yeni tanı alan AIT prevalansı kontrollerle benzerdi (p>0,05). Prolaktinomalı hastalarda B12 vitamini eksikliği kontrollere göre daha yüksekti (%25,6 ve %9,1, p=0,016). Otoantikor pozitifliği gruplar arasında benzer bulundu (%35,7 ve %28,1, p=0,25). Prolaktinomalı hastalarda serum BAFF ve APRIL düzeyleri kontrollerden farklı değildi (p>0,05). AIT olan ve olmayan hastalar ile herhangi bir otoantikor pozitifliği olan ve olmayan hastalar arasında yaşam kalitesi, anksiyete ve depresyon skorları farklı değildi (p>0,05).

Sonuç: Çalışmamızda hastaların üçte birine AİT tanısı konuldu ve hastaların dörtte birinde B12 vitamini eksikliği vardı. Ancak prolaktinomalı hastalarda tiroid dışı otoimmün hastalıklar artmadı ve serum BAFF/APRIL düzeylerinde değişiklik saptanmadı.

Anahtar Sözcükler: Prolaktinoma, otoimmün tiroidit, B12 vitamini, BAFF, APRIL, yaşam kalitesi, anksiyete, depresyon

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INTRODUCTION

Prolactinoma is the most common functional adenoma of the pituitary gland. It develops from the lactotrophic cells of the pituitary gland and secretes prolactin (PRL). Furthermore, it represents the most common cause of pathological hyperprolactinemia. Although the prevalence of prolactinoma varies according to gender and age, it is more common in women and between the ages of 20 and 50 years (1,2).

PRL acts by binding to PRL receptors (PRLR), which belong to the type 1 hematopoietic cytokine receptor superfamily. PRLR can be identified in various tissues, including immune cells, and this abundance of receptors is responsible for the wide range of biological effects observed (3,4). PRL functions as a cytokine-hormone in the immune system and plays a role in immunomodulation via its autocrine-paracrine effects in many tissues. PRL strongly persuades innate and adaptive immune responses, managing the maturation of CD4- CD8- thymocytes to CD4+ CD8+ T-cells through interleukin-2 (IL-2) receptor expression. A direct correlation between PRL levels and the number of B and CD4+ T lymphocytes has been reported (5). It is capable of changing Th1- and Th2-type cytokine production, promoting IL-6 and interferon (INF)-γ secretion, and playing a regulatory role in IL-2 levels. This structural similarity between PRL and the members of the hematopoietic cytokine family, as well as its pro-inflammatory effects occurring via binding to PRLR on T-lymphocytes, B-lymphocytes, and macrophages, suggests that hyperprolactinemia is associated with the development and activity of several autoimmune diseases (6,7). A high frequency of hyperprolactinemia has been reported in patients with systemic lupus erythematosus (SLE) and is associated with disease activity (8). Thyrotropin-releasing hormone has a stimulating effect on the *PRL* gene and thyroid gland. The increase in PRL levels and thyroid-stimulating hormone (TSH) secretion explains the positive correlation between hyperprolactinemia and hypothyroidism (9). In addition, PRL can cause thyroid autoimmunity by regulating B-cell tolerance and increasing autoantibody and immunoglobulin (10). Hashimoto's thyroiditis has been proposed as an autoimmune disease associated with hyperprolactinemia (11).

The regulation of macrophage functions by an endogenous dopaminergic tone suggests that the effects of prolactin on the immune system may be mediated by macrophages (12). BAFF (B-cell activating factor), which is mainly expressed by monocytes, macrophages, and activated T-lymphocytes, and APRIL (a proliferation inducing ligand), which is a homologous factor acting through the same pathway as BAFF, have been shown to be involved in the pathogenesis of certain autoimmune disorders. Elevated levels of BAFF and APRIL in autoimmune conditions are also thought to correlate with disease severity and pathogenic antibody levels. Therefore, these molecules have been identified as potential therapeutic targets in some autoimmune diseases (13,14).

Psychological stress may have a negative impact on healthand can also contribute to the development of autoimmune diseases (1). It is thought that changes in the cytokine production axis with the effect of neuroendocrine hormones triggered by stress may cause immune dysregulation and ultimately autoimmune diseases (15). Stress is associated with an increased frequency of depression (16). On the other hand, the quality of life in patients with prolactinoma is impaired due to secondary hypogonadism, signs due to mass effect, hypopituitarism, and treatment-related side effects (17). Quality of life has been negatively associated with depression and anxiety scores in female patients with prolactinoma (18).

In this study, our objective was to demonstrate whether there is a potential increase in the prevalence of thyroid and non-thyroid autoimmune diseases in women with prolactinoma, to assess the alterations of serum BAFF and APRIL levels as indicators of increased autoimmunity, and to investigate the potential associations with disease markers. Furthermore, a possible relationship between psychological well-being parameters such as quality of life, depression, anxiety, and autoimmune diseases in patients with prolactinoma was evaluated in comparison with control subjects.

MATERIALS AND METHODS

The minimum number of patients was determined using the G Power 3.9.1.4 program for the study, which was planned to be performed with a 95% power 0.05 Type 1 error before patient recruitment. This study was undertaken with the inclusion of 56 female patients followed up at the Outpatient Unit, Department of Endocrinology and Metabolism, Medical Faculty of Gazi University. Only premenopausal female patients with prolactinoma were included. Conditions associated with non-pituitary hyperprolactinemia, such as pregnancy and breastfeeding, nipple stimulation, medication use (such as antidepressant and anticonvulsant drugs), or chronic diseases, were excluded. Fifty healthy premenopausal women attending the Outpatient Unit, Department of Internal Medicine, Medical Faculty of Gazi University for general health control were included as controls. The exclusion criteria for controls were a known thyroid or any other chronic disease.

Laboratory examinations included a recent PRL measurement, macroprolactin recovery level (PEG precipitation), vitamin B_{12} level to diagnose pernicious anemia, follicle stimulating hormone, luteinizing hormone, and estradiol (E_2) levels during the follicular phase of menstruation (ECLIA assay) to diagnose primary ovarian failure and menopause, autoimmune markers including anti-nuclear antibody (ANA), rheumatoid factor immunglobulin (Ig)M (RF-IgM), anti-double-stranded DNA (anti-dsDNA), anti-transglutaminase IgA (anti TG-IgA), and anti-Sjogren's syndrome-A (anti-ssA) (ELISA assay; Orgentec), and elevated serum BAFF and APRIL levels in support of autoimmunity (eBioscience-Human BAFF/APRIL Instant ELISA kits). To assess thyroid function and AIT, ECLIA assays were used to measure TSH, free T_3 (fT_3), free T_4 (fT_4), anti-thyroid peroxidase antibody (anti-TPO), and anti-thyroglobulin antibody (anti-Tg). In addition, thyroid Doppler ultrasound (US) was performed by the same endocrinologist in all patients. The diagnosis of AIT was based on the presence of positive anti-TPO and/or anti-Tg antibodies and/or on the presence of typical US changes such as diffuse reduction in the echogenicity of the thyroid parenchyma and parenchymal heterogeneity (19).

In both patients and control subjects, signs and symptoms suggestive of accompanying autoimmune disorders, vitamin B_{12} deficiency, or thyroid disease were also inquired, such as paresthesia in the extremities, myalgia, arthralgia, skin rash, dry mouth, dry eye, oral aphthous ulcers, genital aphthous ulcers, dizziness, and loss of balance.

Face-to-face interviews were also administered by the same investigator to each participant for short-form 36 (SF-36), Beck Depression Inventory, and Beck Anxiety Inventory to assess the quality of life, depression, and anxiety.

The study protocol was approved by the ethics committee of our university. All study subjects provided written and oral informed consent after adequate information on the purpose and procedures of the study was provided.

Statistical Analysis

All study data were examined using SPSS software (Statistical Package for Social Sciences for Windows) version 22.0. Descriptive statistics for continuous variables included mean ± standard deviation and median (minimum-maximum), whereas categorical variables were expressed as numbers (percentage). The distribution of the continuous variables was tested using the Shapiro-Wilk test. Data with normal distribution were compared between the study groups using the t-test, whereas data without normal distribution were compared using the Mann-Whitney U test. Between-group comparisons for nominal variables (cross-tables) were performed using chi-square and Fisher's exact tests. For comparisons involving more than two groups, the difference between the groups was tested using Kruskal-Wallis analysis of variance. For all comparisons, the statistical level of significance was set at p=0.05.

RESULTS

Among the 56 patients with prolactinoma, the mean duration of disease was 7.0±4.2 years. Overall, 67.9% had a microadenoma and 32.1% had a macroadenoma, with a median adenoma size of 7 mm (2.5-20 mm). Of the subjects with prolactinoma, 57.1% were currently being treated with cabergoline, whereas 28.6% were in remission after appropriate treatment. On the other hand, 14.3% of the patients were not in remission and were not receiving treatment due to several reasons, such as failure to attend follow-up visits or unwillingness to continue treatment. Previous treatments in patients in remission who were not currently receiving treatment included cabergoline in 87.5%, bromocriptine in 8.3%, and bromocriptine followed by cabergoline in 4.2%. The average duration of cabergoline treatment was 48 months (1-240 months), with a median treatment dose of 1 mg/week (0.5-8 mg/week). Central hypothyroidism was in 3.6% of patients with prolactinoma, and all these patients were euthyroided with proper treatment. One patient was receiving treatment with desmopressin because of central diabetes insipidus. Other than these patients, there were no cases of hypopituitarism.

Table 1 shows the demographic characteristics and AIT-related data of patients and controls. The groups were comparable with respect to age (p=0.70). Body mass index (BMI) in patients with prolactinoma was slightly higher than that in controls (p=0.022). As indicated in Table 1, AIT was detected in 32.1% of the patients with prolactinoma, which was one-third of the patients. Hashimoto's thyroiditis was the diagnosis of all subjects with AIT, and none of the subjects had Graves' disease. All patients with AIT in the control group (8.0%) were newly diagnosed individuals, whereas this ratio was 8.9% among the patient group, which was non-significant (p>0.05). Patients with prolactinoma with a known diagnosis of AIT were receiving treatment with levothyroxine (LT_4) because of hypothyroidism (23.2%), whereas no control subjects received such treatment (p<0.001). Only 3.6% of the patients had subclinical

Table 1. Demographic data, descriptive statistics for autoimmune thyroiditis, and comparisons between prolactinoma patients and healthy controls

	Prolactinoma	Controls	p
Age (years)	35.5±9.0	34.8±9.2	0.70
BMI (kg/m^2)	25.2±4.1	23.2±3.6	0.02
Known AIT, n (%)	13 (23.2)	-	
Newly diagnosed AIT, n (%)	5 (8.9)	4 (8.0)	1.00
AIT (known + newly diagnosed), n (%)	18 (32.1)	4 (8.0)	0.002
Hypothyroidism (subclinical), n (%)	2 (3.6)	-	
Receiving LT_4 treatment for primary hypothyroidism, n (%)	13 (23.2)	-	
TSH (mIU/mL)	1.9 (0.3-5.4)	1.8 (0.5-4.8)	0.52
fT_4 (ng/dL)	0.8 (0.5-1.1)	0.8 (0.6-1.1)	0.27
fT_3 (IU/mL)	3.2 (0.3-4.3)	3.2 (2.6-4.1)	0.87
Thyroid volume (mL)	9.6 (5.9-25.7)	9.9 (4-22.3)	0.76
Anti-TPO positivity n (%)	9 (16.1)	3 (6)	0.10
Anti-Tg positivity n (%)	4 (7.1)	1 (2)	0.36
Anti-TPO and/or anti-Tg positivity, n (%)	11 (19.6)	4 (8)	0.08
Thyroid parenchyma heterogeneity	20 (37.7)	11 (22)	0.08
Decreased thyroid parenchymal echogenicity, n (%)	15 (28.3)	6 (12)	0.04
Nodular goiter, n (%)	10 (18.9)	5 (10)	0.20
Non-autoimmune rheumatoid disorder, n (%)	3 (5.4)	-	0.24

AIT: Autoimmune thyroiditis, BMI: Body mass index, LT4: Levothyroxine, TSH: Thyroid-stimulating hormone, fT3: Free T3, fT4: Free T4, Anti-TPO: Anti-thyroid peroxidase antibody, Anti-Tg: Antithyroglobulin antibody.

hypothyroidism, the rest were euthyroid in the patient group, and nobody had hypothyroidism in the control group (p>0.05). The positivity rates for thyroid autoantibodies were comparable across the groups (19.6% in the patient group and 8.0% in the control group, p>0.05).

On the other hand, reduced parenchymal echogenicity, a typical US finding for AIT, was significantly more common in the patient group (p=0.04). With regard to thyroid volume and frequency of nodular goiter, the study subjects and controls were comparable (p>0.05). No study participants were diagnosed with non-thyroiditis autoimmune disorders, although 3 individuals (5.4%) in the patient group were diagnosed with ankylosing spondylitis, which is a seronegative inflammatory rheumatoid disease (p>0.05).

Table 2 summarizes the laboratory findings in patients with prolactinoma and controls. Vitamin B12 deficiency was in 25.6% of the patients with prolactinoma and 9.1% of the control group (p=0.016). Among patients with vitamin B12 deficiency, 75.0% reported forgetfulness and approximately 25.0% reported dizziness and loss of balance. Diagnostic and screening tests for AIT and other autoimmune diseases such as ANA, RF-IgM, anti-dsDNA, anti-TG IgA, anti-ssA, anti-TPO, and anti-Tg were comparable across the two groups (p>0.05). In one patient with anti-dsDNA positivity and another patient with anti-ssA positivity, which are specific auto antibodies for SLE and Sjögren syndrome, clinical manifestations associated with these disorders were absent.

The patient and control groups were also similar in terms of serum BAFF and APRIL levels (p>0.05). No significant differences were also found in the subgroup analysis involving patients with or without AIT as well as in patients with or without any positivity for any type of autoantibodies (p>0.05).

Positive correlations were found between serum BAFF and duration of disease, duration of treatment, and E_2 levels (p=0.02, p=0.03, p=0.03). There was a correlation between serum APRIL levels and BMI only (p=0.008). In regression analysis, duration of disease, duration of the current treatment course, and E2 were included in the model because of their positive correlations with serum BAFF; also, age, BMI, presence of AIT, and positivity for any autoantibody were included in the model as significant clinical parameters. The results of the regression analysis showed that the duration of disease was a determinant of serum BAFF (R^2=0.44, F=2.71, p=0.03), whereas BMI was a determinant of serum APRIL (R^2=0.34, F=2.22, p=0.01).

A comparison of quality of life, depression, and anxiety scores between patients with prolactinoma and controls showed significantly higher Beck Anxiety Inventory scores [12 (0-43) vs. 5 (2-12)] and Beck Depression Inventory scores [10 (0-30) vs. 7 (0-11)] among the patients (p<0.001). Of the patient population, 30.3% were found to have moderately severe or severe anxiety, whereas no control subjects were diagnosed with anxiety (p<0.001); similarly, moderately severe or severe depression was present in 21.4% of the patients, vs. no subjects in the control group (p<0.005). The scores for the general wellbeing domain of the SF-36 quality of life questionnaire were 52.5±18.0 vs. 68.0±17.6 among patients and controls, with the difference being significant (p<0.001). In addition, the respective social functionality scores were 87.5 (25-137) and 75 (25-100), again with a significant difference (p=0.04). On other domains of SF-36, no significant differences were found between the two groups (p>0.05).

Subgroup analyses including patients with or without AIT and patients with or without positivity for any autoantibody did not show

Table 2. Laboratory findings in patients with prolactinoma and healthy controls

	Prolactinoma	Controls	p
FSH (IU/L)	5.8 (2.4-12.3)	6.1 (2.1-16.4)	0.49
LH (IU/L)	4.6 (0.8-13.0)	4.9 (0.7-22.3)	0.46
E_2 (pg/mL)	60 (18-172)	68 (19-301)	0.19
Prolactin (ng/mL)	17.0 (0.3-98.0)	-	
B_{12} deficiency, n (%)	16 (25.6)	4 (9.1)	0.01
BAFF (ng/mL)	0.3 (0.1-0.6)	0.3 (0.1-1.3)	0.94
APRIL (ng/mL)	5.0 (1.2-13.9)	4.1 (0.6-161.4)	0.63
ANA positivity, n (%)	11 (19.6)	4 (12.5)	0.55
RF-IgM positivity, n (%)	3 (5.4)	1 (3.1)	1.00
Anti-dsDNA positivity, n (%)	1 (1.8)	-	1.00
Anti-TG-IgA positivity, n (%)	-	-	-
Anti-ssA positivity, n (%)	1 (1.8)	-	1.00
Anti-TPO positivity, n (%)	9 (16.1)	3 (6)	0.10
Anti-Tg positivity, n (%)	4 (7.1)	1 (2)	0.36
Anti-TPO and/or anti-Tg positivity, n (%)	11 (19.6)	4 (8)	0.08
Autoantibody positivity, n (%)	21 (37.5)	9 (28.1)	0.25

FSH: Follicle stimulating hormone, LH: Luteinizing hormone, E_2: Estradiol, BAFF: B-cell activating factor, APRIL: A proliferation-inducing ligand, ANA: Anti-nuclear antibody, RF-IgM: Rheumatoid factor IgM, anti-dsDNA: Anti-double-stranded DNA, anti-TG-IgA: Anti-transglutaminase IgA, anti-ssA: Anti-Sjogren's syndrome-A, anti-TPO: Anti-thyroid peroxidase antibody, Anti-Tg: Anti-thyroglobulin antibody.

any significant differences with respect to quality of life, anxiety, and depression (p>0.05). Similarly, there was no statistically significant difference between patients with prolactinoma who received active treatment and those who did not (p>0.05).

DISCUSSION

Because of PRLR expression by immune cells, there may be an increased incidence of systemic and organ-specific autoimmune diseases in hyperprolactinemia. SLE, rheumatoid arthritis, primary Sjögren's syndrome, systemic sclerosis, psoriatic arthritis, and Type 1 diabetes mellitus are examples of systemic autoimmune diseases. Organ-specific autoimmune diseases are mainly Grave's disease, Hashimoto's thyroiditis, Addison's disease, celiac disease, and multiple sclerosis (7). In our study, the prevalence of known or newly diagnosed AIT (Hashimoto's thyroiditis) was 32.1% in women with prolactinoma. The percentage of patients under treatment for primary hypothyroidism was as high as 23.2%, indicating that one-fourth of prolactinoma patients were receiving LT_4 treatment. However, the frequency of newly diagnosed AIT was found to be similar to that in control subjects. The frequency of known AIT was not compared because we excluded those with known thyroid disease in the recruitment of controls. In a study by Elenkova et al. (20) examining the frequency of AITD among 154 female patients with prolactinoma and 104 healthy female controls, the reported rates of AITD in the patient and control groups were 29.9% and 10.4%, respectively. They did not specify whether AITD was AIT or Graves' disease (20). Pilli et al. (21) reported AIT in 13.4% and 6.3% of their patient and control subjects; in that study, 108 female and 41 male patients with prolactinoma were included, whereas the control group consisted of 96 patients with non-functional adenoma and no stalk compression potentially associated with PRL elevation as well as 47 sex-matched but not age-matched 47 subjects with a diagnosis of empty sella. Dogansen et al. (22) retrospectively evaluated the frequency of Hashimoto's thyroiditis in 83 patients with prolactinoma and 78 patients with acromegaly and found a higher incidence (33%) in patients with prolactinoma than in those with acromegaly. Onal et al. (23) compared patients with hyperprolactinemia and healthy controls and reported a higher prevalence of thyroid dysfunction, although thyroid autoimmunity was not more frequent.

In the current study, patients with prolactinoma and controls were not significantly different in terms of anti-TPO and anti-Tg levels or positivity rates for these markers. Similarly, there were no significant differences between patients and controls with respect to thyroid autoantibody levels in the study by Pilli et al. (21), although they found an increased rate of AIT in prolactinoma. On the other hand, some others reported an increased frequency of thyroid autoantibody positivity in patients with prolactinoma. For instance, in the study by Elenkova et al. (20), patients with prolactinoma had a 3-fold increase in both anti-TPO and anti-Tg positivity compared with healthy controls; Sayki Arslan et al. (10) observed a 2-fold increase in anti-TPO and anti-Tg positivity in naïve prolactinoma patients as compared to healthy subjects. Although patients with prolactinoma had a high prevalence of AIT among our patient group, no significant differences in thyroid autoantibody and positivity rates were found between patients and controls, and this finding could be related to the fact that 23.2% of the patients with prolactinoma were receiving treatment with LT_4, which could have reduced the production of autoantibodies (24).

To the best of our knowledge, this is the first report investigating the prevalence of both thyroid and non-thyroid autoimmune disorders in women with prolactinoma. The proportion of subjects who tested positive for any autoantibody (ANA, anti-dsDNA, anti-ssA, antiTG-IgA, RF-IgM, anti-TPO, anti-Tg) was 37.5% and 28.1% in our patient and control groups, respectively, with the difference being non-significant. Unlike our study design, in previous studies, an emphasis has been placed on investigating hyperprolactinemia in patients with autoimmune disorders (25-27), generally in the context of assessing PRL levels as well as the association between disease activity and autoantibodies that are used as disease markers. In our study, we aimed to assess the effects of exposure to high PRL during the disease process on the immune system and to assess certain autoantibodies. Additionally, only female patients were included because autoimmune disorders occur more commonly in females than in males. In this regard, our study differs from previous reports. In contrast to the high prevalence of AIT in our study group, we found similar ratios of positivity for any autoantibody among patients and controls as well as the absence of signs of autoimmune disorders in most individuals with autoantibody positivity. This finding did not support our hypothesis of an increased risk of non-thyroid autoimmune disorders in this population. One possible explanation might be that the low prevalence of non-thyroid autoimmune disorders compared with autoimmune thyroid disease in our population may have led to our findings. The other reason may be that some autoantibodies that are markers of autoimmune disorders are non-specific and may also be positive in healthy individuals.

Another topic that we addressed in this study was circulating BAFF and APRIL concentrations in relation to prolactinoma. BAFF and APRIL pathways, which are involved in the maturation, proliferation, and differentiation of B-lymphocytes, are known to be associated with the production of autoantibodies and autoimmune disorders (13). In this study, patients and controls did not differ significantly in terms of serum BAFF and APRIL levels. In addition, no correlation was found between any autoantibody levels and serum BAFF and APRIL levels. These results support our conclusion that the prevalence of non-thyroid autoimmune disease is not increased in patients with prolactinoma. Although the frequency of autoimmune thyroid disease was increased in the patient group compared with that in the controls, the fact that most of them were in remission under LT_4 treatment may be an explanation for this result. In addition, studies supporting this relationship in the literature generally had several cases. The number of patients and controls in our study may have been insufficient to detect the specified correlations. This result supported our finding that the prevalence of non-thyroid autoimmune disorders did not increase in patients with prolactinoma. Nevertheless, a positive correlation was observed between serum BAFF and E_2 levels. Gender is the single most important risk factor for many autoimmune disorders. Previous investigations have shown that female hormones may augment autoimmunity through their effects on B-lymphocytes. In the study by Drehmer et al. (28), where BAFF expression in 34 healthy male and female individuals was investigated, no differences were found in BAFF expression between male and female subjects under normal conditions, but stimulation of cells with E_2 resulted in a significant elevation of BAFF expression. Similarly, Fan et al. (29) established an association between E_2 and BAFF in a murine model. Despite the

association between E_2 and BAFF, a possible link between PRL and BAFF has not been demonstrated in our study, although both are known to play a role in the development of autoimmune diseases because of their immunomodulatory effects.

According to our findings, patients with prolactinoma had increased Beck Anxiety Inventory and Beck Depression Inventory scores, with increased frequency and severity of anxiety and depression in these subjects. Furthermore, as evidenced by SF-36 assessments, patients with prolactinoma had a lower self-perception of general health. Although most previous studies used SF-36, we also included anxiety and depression assessments in this group of patients. When the prolactinoma patients with and without AIT or autoimmune disorder were compared with respect to anxiety, depression, and quality of life, no significant differences were found. These data suggested that the main factor responsible for unfavorable effects on quality of life, anxiety and depression was the presence of prolactinoma not autoimmune diseases.

Study Limitations

The limitation of our study is the cross-sectional design. We believe that prospective long-term follow-up of our patients would provide more clear information on the development of autoimmune disorders.

CONCLUSION

The risks of AIT and non-thyroid autoimmune disease were not increased in women with prolactinoma, nor were serum BAFF/APRIL levels altered compared with healthy controls. Higher rates of depression and anxiety, as well as a lower quality of life, were associated with the presence of prolactinoma, but not with AIT or non-thyroid autoimmune diseases.

Ethics

Ethics Committee Approval: Approval was granted by the Ethics Committee of Gazi University (approval number: 24074710, date: 08.01.2018).

Informed Consent: Informed consent was obtained from all participants included in the study.

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Authorship Contributions

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