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The higher incidence of autoimmune thyroid disease in prolactinomas than in somatotrophinomas

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ABSTRACT

Objective: Many studies have shown that prolactin (PRL) plays an important role in autoimmune diseases. The aim of this study was to compare the current frequency of autoimmune thyroid disease (ATD) in prolactinomas with another type of functional pituitary adenoma (FPA), somatotrophinoma. Another aim of the study was to evaluate possible factors related to thyroid autoimmunity and the process of ATD in FPAs.
Methods: We retrospectively evaluated the presence of thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) and thyroid morphologic findings in our patients with FPA (78 with acromegaly and 83 with prolactinoma). The relationship of autoantibody positivity with baseline PRL levels, activity of acromegaly, and treatment of dopamine agonists (DA) and hypogonadism was also assessed. Patients with ATD and hypothyroidism due to autoimmune thyroiditis were also evaluated.
Results: ATD (Hashimoto's thyroiditis) was detected more frequently in patients with prolactinoma than in patients with acromegaly (33% and 17%, respectively; $p = 0.01$). Thyroid autoantibody positivity was found more frequently in females in the whole group ($p = 0.02$) and in the acromegaly group ($p = 0.008$). There was no difference according to sex among the patients with prolactinoma ($p = 0.800$). ATD was found not to be related with baseline PRL levels, treatment of DA, and presence of hypogonadism ($p = 0.232$, $p = 0.435$, $p = 0.464$, respectively) in the prolactinoma group, and activity of acromegaly, presence of hypogonadism in the acromegaly group ($p = 0.753$, $p = 0.654$, respectively). Autoimmune hypothyroidism was more frequent in the prolactinoma group than in the acromegaly group among patients with thyroid autoantibody positivity ($p = 0.004$).
Conclusion: Thyroid autoantibodies should be evaluated both at the time of diagnosis and during the course of treatment in patients with prolactinoma, and thyroid function tests should be closely monitored in patients with autoantibody positivity.

1. Introduction

Prolactin (PRL) is secreted from lactotroph cells of the anterior pituitary gland and also from some extrapituitary tissues, such as immune cells, neurons, prostate, decidua, breast, and skin [1]. PRL is also structurally similar to members of hematopoietic cytokine family, and PRL plays a proinflammatory role by binding to PRL receptors (PRL-R) located on T lymphocytes, B-lymphocytes, and macrophages [2]. PRL causes immunoglobulin and antibody production by stimulating immune cells via its receptors [3]. Many studies have shown that PRL plays an important role in autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, primary Sjögren's syndrome, type 1 diabetes mellitus, systemic sclerosis, Addison's disease, pernicious anemia, primary biliary cirrhosis, celiac disease, myasthenia gravis, and autoimmune thyroid disease (ATD) [4]. Pelkonen et al. [5] were the first to review the relationship between hyperprolactinemia and ATD. Later, Ferrari et al. [6] found that the prevalence of thyroid autoantibody positivity was significantly higher in patients with prolactinoma than controls. Most studies since that time have shown that the incidence of ATD is increased in hyperprolactinemia [7–11].

Acromegaly is frequently associated with the presence of goiter, especially nodular goiter, but the prevalence of ATD is reported low [12–15]. However, one study reported that the frequency of ATD was higher in patients with acromegaly compared with the general population [16].

In the literature, one study has compared the presence of thyroid autoantibodies between prolactinomas and somatotrophinomas [10].

Abbreviations: AA, active acromegaly; ATD, autoimmune thyroid disease; CA, cured acromegaly; DA, dopamine agonist; ECLIA, electrochemiluminescent immunoassay; FPA, functional pituitary adenoma; GH, growth hormone; IGF-1, insulin growth factor-1; LT4, levothyroxine; PRL, prolactin; PRL-R, PRL receptors; SD, standard deviation; Th, T helper; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; USG, ultrasonography; WCA, well-controlled acromegaly.

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However, in that old study, only the frequency of ATD and the peripheral lymphocyte population type were compared and some patients with hyperprolactinemia were also included into the acromegaly group; no evaluation according to clinical findings and follow-up was made. Hyperprolactinemia accompanying acromegaly may have affected the evaluation in that study. Therefore, we aimed to evaluate the current frequency of ATD in functional pituitary adenomas (FPA), such as pure prolactinoma and pure growth hormone (GH)-secreting adenomas, the possible factors related to autoimmunity, and the progress of ATD.

2. Material and method

This study was a retrospective analysis of patients with FPA, who were followed up in the pituitary out-patient clinic of the university hospital of Istanbul Medical Faculty. A total of 161 patients, including 78 patients with acromegaly and 83 patients with prolactinoma, were evaluated. The diagnosis of prolactinoma or acromegaly was made according to the typical clinical signs and symptoms and radiographic findings (pituitary adenoma confirmed through magnetic resonance imaging (MRI)) and laboratory tests (high PRL levels in at least two different samples, high insulin growth factor-1 (IGF-1) levels according to age-sex and nonsupressible GH levels by oral glucose tolerance test) in accordance with the current guidelines [17–19]. Patients with factors that caused secondary hyperprolactinemia such as primary hypothyroidism, lactation, drug-induced hyperprolactinemia, or chronic renal disease were excluded from the study. High PRL levels in patients with acromegaly or those with PRL positivity in immunohistochemical specimen examinations after surgery were also excluded from the study. Moreover, patients with prolactinoma found to have central hypothyroidism that developed after operation and/or radiotherapy were not included into the study.

Sex, age at diagnosis, baseline PRL levels, baseline tumor diameter, duration of follow-up, baseline thyroid status, findings of thyroid ultrasonography (USG), thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TgAb) tests were evaluated retrospectively for every patient.

Serum PRL levels were measured using an electrochemiluminescent immunoassay (ECLIA) with the normal range for adult males and females of 4.04–15.2 ng/mL and 4.7–23.3 ng/mL, respectively. TPOAb and TgAb were measured using ECLIA with normal ranges for TPOAb and TgAb (0–34 IU/mL and 0–115 IU/mL, respectively). Radiologists experienced in sonography conducted the thyroid examinations using different sonographic equipment (SI 400, Siemens, Erlangen, Germany; Logic 7, GeneralElectric, Milwaukee, Wisconsin; Sonoline Antares, Siemens) with high-frequency (13 MHz) linear probes. Patients with at least one positive antibody (TPOAb > 34 IU/mL and/or TgAb > 110 IU/mL) and the presence of sonographic signs of ATD (heterogeneity, hypoechogenity, and pseudonodular image of the thyroid paranchyma) were accepted as having ATD. Nodular goiter was determined using USG and a nodule was defined as a certain formation exceeding 5 mm in diameter [20]. Pseudonodular images of ATD was excluded from this definition. Nodules detected only by palpation were also excluded. Patients with at least one nodule and who met the criteria mentioned above were accepted to have nodular goiter disease.

Patients with prolactinoma and patients with acromegaly were compared in terms of thyroid autoimmunity and the presence of nodular goiter. Patients with ATD and hypothyroidism due to autoimmune thyroiditis and receiving levothyroxine (LT4) replacement therapy were evaluated. Frequencies of thyroid antibody positivity and nodular goiter according to sex were evaluated. Patients with prolactinoma were divided into two groups, as antibody positive and negative groups. These two groups were compared with each other according to age at diagnosis, baseline PRL levels, duration of follow-up, frequency of hypothyroidism development, and mean duration to the development of hypothyroidism. Also, the relation of thyroid antibody presence and continued hypogonadism due to drug resistance or permanent hypogonadism was evaluated. Patients with naïve prolactinoma (before dopamine agonist-DA-treatment) and patients treated with DA were compared for ATD frequency.

The course of ATD and nodular goiter in patients with acromegaly and the frequency of hypothyroidism, either due to autoimmunity or other causes in patients with acromegaly were also evaluated. The frequency of ATD was evaluated according to the presence of permanent hypogonadism and activity of acromegaly.

Statistical analyses were performed using SPSS version 21.0. Categorical variables were defined by frequency and percentage rate, and numeric variables with mean ± standard deviation (SD). In dual in dependent group comparisons, Student's *t*-test was used for normally distributed numeric variables and the Mann-Whitney *U* test was used for non-normally distributed data. Categorical variables were compared using the Chi-square test. A p value of <0.05 was accepted as statistically significant.

3. Results

Seventy-eight patients with acromegaly (40 women and 38 men) and 83 patients with prolactinoma (60 women and 23 men) were included in the study. The mean age at diagnosis was 32.3 ± 11.8 years (range, 18–71 years) and the mean follow-up time was 72.5 ± 50.5 months (range, 6–257 months) in the prolactinoma group. At the initial assessment, the mean size of adenoma was 15.8 ± 10.4 mm (range, 5–52 mm) and the mean PRL levels were 1120.4 ± 2676.2 ng/dL (range, 105–18,500 ng/dL) in the prolactinoma group. The mean age at diagnosis was 42.3 ± 12.5 years (range, 19–72 years) and the mean follow-up time was 83.5 ± 55.8 months (range, 20–244 months) in the acromegaly group. At the initial assessment, the mean size of adenoma was 15.9 ± 7.5 mm (range, 5–40 mm) in the acromegaly group. Female sex was found to be more common and the mean age at diagnosis was found to be younger in the prolactinoma group than in the acromegaly group ($p = 0.006$ and $p < 0.001$, respectively). The mean follow-up time was not statistically different between groups. Thyroid autoantibody positivities were 25% (40 of 161 patients) in the whole group, 33% (27 of 83 patients) in the prolactinoma group and 17% (13 of 78 patients) in the acromegaly group. The frequency of nodular goiter was 42% (68 of 161 patients) in the whole group, 18% (15 of 83 patients) in the prolactinoma group and 68% (53 of 78 patients) in the acromegaly group. Nodular goiter was found significantly higher in the acromegaly group, whereas thyroid autoantibody positivity was significantly higher in the prolactinoma group ($p < 0.001$ and $p = 0.01$, respectively). Nineteen of the 27 patients with autoantibody positivity in the prolactinoma group (70%) and 3 of the 13 patients with autoantibody positivity in the acromegaly group (23%) developed autoimmune hypothyroidism, each received LT4 replacement therapy. Autoimmune hypothyroidism was more common in the prolactinoma group than in the acromegaly group ($p = 0.004$). The comparisons of demographic and thyroid features of prolactinoma and acromegaly groups are shown in Table 1.

Thyroid autoantibody positivity was found to be significantly higher in women in the whole group ($p = 0.02$) and in the acromegaly group ($p = 0.008$) but there was no difference in the prolactinoma group according to sex ($p = 0.800$). The presence of nodular goiter was significantly higher in men, both in the whole group ($p < 0.001$) and in the prolactinoma group ($p < 0.001$), but there was no difference according to sex in the acromegaly group ($p = 0.290$). Data of both groups are given in Table 2.

Nine (12%) patients had active acromegaly (AA), 32 (41%) patients were receiving somatostatin analogs and had well-controlled acromegaly (WCA), and 37 (47%) patients had cured acromegaly (CA) in the acromegaly group. Two (15%) patients had AA, 6 (46%) patients had WCA and 5 (39%) patients had CA in the patients with positive thyroid autoantibodies. There was no significant relationship between thyroid