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Nodular Thyroid Disease and Papillary Thyroid Carcinoma in Functional Pituitary Adenomas

Fonksiyonel Hipofiz Adenomlarında Nodüler Tiroid Hastalığı ve Papiller Tiroid Kanseri

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Abstract

Objective: Increased frequency of nodular thyroid disease has been reported in acromegalic patients. Recent studies have also demonstrated an increased co-existence of nodular thyroid disease with Cushing's disease and prolactinoma. In this study, we evaluated the frequency and outcomes of nodular thyroid disease in each type of functional pituitary adenoma.

Material and Methods: A total of 232 patients diagnosed with acromegaly (n=138), prolactinoma (n=59) or Cushing's disease (n=35) were included in this retrospective observational study. The frequency of nodular thyroid disease, fine-needle aspiration results, and the frequency of papillary thyroid carcinoma were compared in each group. Factors related to nodule development were evaluated in functional pituitary adenoma patients with or without nodules.

Results: Nodular thyroid disease frequency was higher in patients with acromegaly (69%) compared to those with prolactinoma (36%) or Cushing's disease (34%) (p<0.001). Fine-needle aspiration results and PTC frequencies were similar between the groups. In comparison to patients without nodules (n=104), those with nodules (n=128) were older (p=0.01) and had a higher incidence of glucose metabolism disorders (p=0.006). Insulin-like growth factor-1 levels were higher in acromegalic patients with nodular thyroid disease (p=0.01). There was no relationship between nodule formation and baseline prolactin or cortisol/adrenocorticotropic hormone levels in the patients with prolactinomas and Cushing's disease, respectively.

Conclusion: Although nodular thyroid disease was more common in acromegalic patients, its incidence in patients with prolactinoma and Cushing's disease were higher than previously reported in our country (23.5%). The most important factors affecting nodule formation in functional pituitary adenoma patients were glucose metabolism disorders and age. Although a higher frequency of PTC has been reported in acromegalic patients, it was similar for all functional pituitary adenoma patients in our study.

Keywords: Acromegaly; prolactinoma; Cushing's disease; thyroid nodule; papillary thyroid carcinoma

Özet

Amaç: Akromegaliklerde nodüler tiroid hastalığı sık görülmesine rağmen, Cushing hastalığı ve prolaktinomalarında artmış sıklığını gösteren yayınlar mevcuttur. Bu nedenle; her bir fonksiyonel hipofiz adenomu, nodüler tiroid hastalığı görülme sıklıkları ve takip sonuçları açısından karşılaştırdık.

Gereç ve Yöntemler: Bu çalışma, fonksiyonel hipofiz adenomu tanılı toplam 232 hastanın (138 akromegali, 59 prolaktinoma ve 35 Cushing hastalığı) dahil edildiği retrospektif gözlemsel bir çalışmadır. Her bir fonksiyonel hipofiz adenomu için nodüler tiroid hastalığı görülme sıklıkları, tiroid ince iğne aspirasyon biyopsisi, cerrahi sonuçları ve papiller tiroid kanseri görülme sıklıkları kaydedilmiştir. Nodülü olan ve olmayan hastalar nodül gelişimiyle ilişkili olabilecek parametreler açısından karşılaştırılmıştır.

Bulgular: Nodüler tiroid hastalığı; akromegaliklerde (%69), prolaktinomalar (%36) ve CH olanlara (%34) göre daha yüksek (p<0,001) olmasına karşın, tiroid ince iğne aspirasyon biyopsisi sonuçları, ve papiller tiroid kanseri saptanma oranları benzer bulundu. Nodülü olan hastalar (n=128), olmayanlara (n=104) göre daha yaşlıydı (p=0,01) ve glukoz metabolizması bozuklukları daha sıktı (p=0,006). Nodüler tiroid hastalığı olan akromegaliklerde bazal insülin benzeri büyüme faktörü-1 düzeyleri daha yüksek (p=0,01) iken nodülü olan ve olmayan prolaktinoma ve Cushing hastalığı olanlarda sırasıyla bazal prolaktin düzeyleri ve kortizol/adrenokortikotropik hormon düzeyleri benzer saptandı.

Sonuç: Akromegaliklerde nodüler tiroid hastalığı sıklığı artmasına karşılık, diğer iki grup için bulduğumuz sıklıklar da ülkemiz için bildirilenlerin (%23,5) üzerindedir. Glukoz metabolizması bozuklukları ve ileri yaş, tüm gruplar için nodül gelişiminde en önemli faktörlerdir. Akromegaliklerde artmış papiller tiroid kanseri sıklığı birçok yayında bildirilmesine rağmen, serimizde papiller tiroid kanseri görülme sıklığı her bir fonksiyonel hipofiz adenomu için benzer bulunmuştur.

Anahtar kelimeler: Akromegali; prolaktinoma; Cushing hastalığı; tiroid nodülü; papiller tiroid kanseri

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Introduction

Nodular thyroid disease (NTD) is a common thyroid disorder with an unclear etiopathogenesis, owing to its complex nature. The most important clinical factors associated with NTD are iodine deficiency, nutritional goitrogens, radiation, smoking, age, gender, and genetics (1). An increased frequency of NTD has also been reported in individuals with functional pituitary adenoma (FPA); acromegaly is more frequently associated with NTD compared to Cushing's disease (CD) or prolactinoma (2-10). However, an increased risk of NTD in patients with CD and prolactinoma has been reported in recent studies (11-15).

Although thyroid nodules are common, only 8-16% of them are malignant (16). Screening for papillary thyroid carcinoma (PTC) is recommended in patients with acromegaly due to their higher risk of developing tumors, but not for prolactinoma and CD patients (2-9, 17-21). We found only one study that evaluated the prevalence of PTC in prolactinomas (12) and one case report on the co-existence of CD and PTC (22).

We detected a higher frequency of NTD in CD and prolactinoma patients in our clinical practice, along with a concurrent increase in PTC diagnosis. Therefore, we aimed to evaluate and compare different FPAs (acromegaly, prolactinoma, and CD) in terms of NTD and PTC frequencies and outcomes. The effect of common metabolic disorders and hormonal excess in each adenoma type that may play role in the etiopathogenesis was also evaluated retrospectively.

Material and Methods

The clinical data and thyroid ultrasonography (USG) results of FPA patients who were followed up in the university hospital pituitary and radiology clinics were evaluated retrospectively. A total of 232 patients (138 female, 94 male) diagnosed with acromegaly (n=138), prolactinoma (n=59) or CD (n=35) were included in this retrospective observational study. The diagnosis of FPA was confirmed with clinical, laboratory, and radiological findings according to the current guidelines (23-25). The absence of cortisol suppression in the dexamethasone suppression tests and high plasma adrenocorticotropic hormone (ACTH) levels, high prolactin (PRL) levels in two separate laboratory measurements, and high insulin-like growth factor-1 (IGF-1) levels (according to age) with non-suppressible growth hormone (GH) levels as per oral glucose tolerance test (OGTT) were used as the laboratory diagnostic criteria for CD, prolactinoma, and acromegaly, respectively. The patients with available thyroid USG results, either at the time of their FPA diagnosis or during the follow-up period, were included in the study. Nodules that were detected only with thyroid palpation without radiological evidence were excluded. Radiologists experienced in sonography conducted the thyroid examinations using different sonographic devices (SI 400, Siemens, Erlangen, Germany; Logic 7, GeneralElectric, Milwaukee, Wisconsin; Sonoline Antares, Siemens) with high-frequency (13 MHz) linear probes. NTD was determined using USG and a nodule was defined as an outgrowth exceeding 5 mm in diameter (26). Pseudonodular images were excluded from this definition. Patients with at least one nodule and who met the criteria mentioned above were confirmed to have NTD.

Dominant nodule size, the presence of single or multiple nodules, as well as USG features were evaluated. Fine-needle aspiration (FNA) was performed in nodules >1 cm or ≤1 cm with suspicious features such as microcalcifications, irregular borders, hypoechogenicity, a length longer than width or absence of nodule halo. The nodules were classified as nondiagnostic (category 1, with same subsequent FNA results), benign (category 2), suspicious (category 3 and 4) or malignant (category 5 and 6) on the basis of at least one FNA, and according to the BETHESDA 2007 classification (27).

In patients those had surgical intervention, the operation indications were evaluated. Patients with PTC in pathology results were analyzed, and the presence of PTC in NTD patients was separately recorded for each group. Tall-cell, hobnail, solid and diffuse sclerosan variants are indicated as high-risk subtypes for PTC. The rates of radioactive iodine (RAI) treatment and the presence of PTC remission on the patient's last visit were evaluated. Thus, NTD was compared according to ultrasonographic features, FNA

results, surgical outcomes, and the presence of PTC in acromegaly, CD and prolactinoma patients.

The FPA patients with or without NTD were compared according to their sex, age at diagnosis, maximum adenoma diameter, TSH levels (excluding central hypothyroidism), glucose metabolism disorders (patients with diabetes mellitus or pre-diabetes), fasting plasma glucose (FPG) levels, HbA1c, and homeostasis model assessment of insulin resistance (HOMA-IR) at initial assessment. Pre-diabetes was defined as impaired fasting glucose (IFG) [FPG between 100-125 mg/dL (5.6-6.9 mmol/L)] and/or impaired glucose tolerance (IGT) [(OGTT 2 h plasma glucose between 140-199 mg/dL (7.8-11 mmol/L)], and/or HbA1c between 5.7-6.4%. Diabetes mellitus (DM) was defined when FPG >126 mg/dL (7 mmol/L), OGTT 2 h plasma glucose >200 mg/dL (11.1 mmol/L), and HbA1c >6.4% (28, 29). The HOMA-IR was calculated with the formula: [fasting insulin (μU/mL)×FPG (mmol/L)]/22.5. HOMA-IR values higher than 2.5 indicated insulin resistance (IR) (30). Acromegalic patients with or without nodules were compared according to baseline GH levels, IGF-1% ULN (corresponding to the percentage of increase compared with the upper limit of normal), and the presence of colonic polyps. The patients with or without NTD were compared according to baseline PRL levels or baseline ACTH-cortisol levels, and the results of cortisol with a low dose dexamethasone suppression test in prolactinoma and CD patients, respectively.

Assays

GH and IGF-1 levels were measured using a two-site chemiluminescent immunometric assay (*Immulite* 2000). Serum PRL levels were measured using an electrochemiluminescent immunoassay (ECLIA). Serum cortisol and ACTH levels were measured using an electrochemiluminescent immunoassay (*Roche Hitachi*) and a chemiluminescence immunoassay (*Immulite 2000*) respectively. ***Statistical analyses*** were performed using SPSS version 21.0. Categorical variables were presented as frequency and percentage, and numerical variables as mean ± standard deviation (SD). In dual independent group comparisons, Student's t-test was used for normally distributed numeric variables and the Mann-Whitney U test for non-normally distributed data. In triple independent group comparisons, ANOVA was used for normally distributed numeric variables and Kruskal-Wallis test for non-normally distributed data. Categorical variables were compared using the Chi-square test. The predictors of presence of NTD were assessed by a multivariate binary logistic regression analysis. Variables with p-value <0.05 in univariate analysis were included in the multivariate analysis model. Statistically significant results were defined with a p-value <0.05.

Results

CD was more common among the female patients (p=0.009) and the age at diagnosis was higher in acromegaly patients (p<0.001). The prevalence of NTD was higher in the acromegalic patients (69%) compared to prolactinoma (36%) and CD (34%) patients (p<0.001). However, the frequency of single or multiple nodules, and dominant nodule sizes were similar between the groups. In patients with NTD, FNA cytology results and surgical indications were similar in each FPA group. The frequency of PTC in all patients was similar (10.8% for acromegaly, 3.4% for prolactinomas and 11.4% for CD), as were the largest PTC tumor diameter, high-risk subtype and RAI treatment rates (Table 1).

Compared to patients without nodules, those with nodules were older (p=0.01), had a higher incidence of glucose metabolism disorders (p=0.006), and higher FPG (p=0.014). Although HbA1c and HOMA-IR levels were also higher in patients with nodules, the difference was not statistically significant. In acromegalic patients with NTD, IGF-1% ULN tended to be higher (p=0.01), and colonic polyps were more frequent (p=0.017). There was no relationship between nodule formation and baseline PRL levels in prolactinoma patients, or with baseline ACTH-cortisol and suppressed cortisol levels in CD patients (Table 2).

The patient's age at diagnosis, the presence of glucose metabolic disorders and fasting plasma glucose levels in all patients, and the frequency of colonic polyps and IGF-1 levels in the acromegaly patients were statistically

Table 1. Comparison of functional pituitary adenomas in terms of nodular thyroid disease and papillary thyroid carcinoma.

N=232	Acromegaly (n=138)	Prolactinoma (n=59)	Cushing's Disease (n=35)	p
Sex (Male/Female)	65/73	22/37	7/28	**0.009***
Age at diagnosis (years) mean±SD	42±13	36±13	36±11	**<0.001º**
Frequency of nodular thyroid disease (n,%)	95 (69)	21 (36)	12 (34)	**<0.001º**
Single nodule (n)/Multiple nodules (n)	20/75	7/14	6/6	*NS*
Dominant nodule size (mm) mean±SD	17.4±9.7	15.5±10.3	14.5±6.7	*NS*
FNA cytology (n,% of patients with nodules)	55 (58)	10 (48)	8 (67)	*NS*
Benign (n,%)	36 (66)	8 (80)	3 (38)	
Suspicious (n,%)	9 (16)	1 (10)	2 (25)	
Malignancy (n,%)	6 (11)	-	2 (25)	
Nondiagnostic (n,%)	4 (7)	1 (10)	1 (12)	
Surgery (n,% of patients with nodules)	27 (28)	3 (14)	5 (42)	*NS*
Suspicion of malignity	13 (48)	2 (67)	5 (100)	
Increased nodule size	8 (30)	1 (33)	-	
Intrathoracic goiter	4 (15)	-	-	
Thyrotoxicosis	2 (7)	-	-	
Frequency of papillary thyroid carcinoma (n,% of all patients)	15 (10.8)	2 (3.4)	4 (11.4)	*NS*
Largest tumor diameter (mm) (mean±SD)	11±9 (1–30)	26±12 (17–35)	21±9 (14–9)	
High-risk subtype (n,%)	1	0	1	
RAI therapy (n,%)	9	2	4	
Remission rate at last visit (n,%)	14 (93)	2 (100)	4 (100)	

p<0.05, statistically significant, Significant p values are shown in bold.
FNA; fine needle aspiration, RAI; radioactive iodine therapy.
*: Acromegaly & Cushing's Disease; º: Acromegaly & Cushing's Disease, acromegaly & prolactinoma.

significant in univariate analysis, but not in multivariate binary logistic regression analysis. Therefore, these factors were not independent predictors of NTD (Table 3).

Discussion

The frequency of NTD was higher in acromegaly patients in our study. To the best of our knowledge, no study so far has compared NTD frequency in FPAs; however, previous studies on patients with acromegaly reported an increased prevalence of NTD compared to the general population (2-10). This is consistent with our study, which found an incidence rate of nearly 60% NTD in acromegalic patients. In addition, NTD prevalence was 36% and 34% in prolactinoma and CD patients, respectively, which is higher than previously reported for individuals under 65 years of age in our country (23.5%) (31). One reason for this could be that routine thyroid USG was not performed in these patients, and every patient with a neck USG due to any other reason, including suspicious findings during thyroid palpation, was included in this study. However, in two recent studies, an increased frequency of NTD was reported in prolactinoma patients (11, 12), and two other studies demonstrated increased NTD frequency in patients with CD compared to the general population (14, 15).

Although NTD was more common in patients with acromegaly, dominant nodule size and distribution of single or multiple nodules were similar in all three groups. In addition, FNA and surgery rates and outcomes were also similar. The most important finding of our study was the similar frequencies of PTC between the groups. It is well known that despite the prevalence of thyroid nodules, only 8-16% of these nodules are malignant

Table 2. Comparison of patients with and without nodule in terms of clinical and laboratory findings.

N=232	Patients with nodule (n=128)	Patients without nodule (n=104)	p
Sex (Male/Female)	52/76	42/62	*NS*
Age at diagnosis (years) mean±SD	42±13	37±13	**0.01**
Max. adenoma diameter (mm) mean±SD	16±10	17±12	*NS*
TSH levelsº (mIU/L) mean±SD	1.9±3	1.9±1.8	*NS*
Glucose metabolism disorders* (n, %)	92 (72)	57 (55)	**0.006**
Fasting plasma glucose (mg/dL) mean±SD	116±41	102±32	**0.014**
HbA1c (%) mean±SD	7.1±1.9	6.4±1.4	*NS*
HOMA-IR mean±SD	4.9±5.1	4.1±3.3	*NS*
Baseline IGF-1% ULN (patients with acromegaly) mean ±SD	334±149	254±82	**0.01**
Baseline GH levels (ng/mL) (patients with acromegaly) mean ±SD	19±17	19±14	*NS*
Colonic polyp (n,%) (patients with acromegaly)	29 (31)	5 (12)	**0.017**
Baseline PRL levels (ng/mL) (patients with prolactinoma) mean±SD	1343±2902	1329±2381	*NS*
Baseline ACTH levels (pg/mL) (patients with Cushing's disease) mean±SD	74±47	85±43	*NS*
Baseline cortisol levels (µg/dL) (patients with Cushing's disease) mean±SD	31±11	28±10	*NS*
Suppressed cortisol levels (µg/dL) (patients with Cushing's disease) mean±SD	18±9	17±9	*NS*

p<0.05 statistically significant, Significant p values are shown in bold
º: TSH level was assessed in patients without central hypothyroidism; *: Patients with diabetes mellitus or prediabetes.
NS, not significant; TSH, thyroid stimulating hormone; HOMA-IR, homeostasis model assessment of insulin resistance; IGF-1, insulin-like growth factor-1; GH, growth hormone; IGF-1% ULN; the % increase compared with the upper limit of normal, PRL, prolactin; ACTH, adrenocorticotropic hormone.

Table 3. Multivariate binary logistic regression analysis for the assessment of independent predictors of nodular thyroid disease.

	Nodular thyroid disease			
	Beta	Standard error	P value	OR (95% CI)
Age at diagnosis	0.017	0.012	0.149	1.017 (0.994-1.041)
Glucose metabolism disorders	0.595	0.341	0.081	1.813 (0.930-3.538)
Fasting plasma glucose	0.005	0.005	0.299	1.005 (0.996-1.014)
IGF-1 levels (patients with acromegaly)	0.002	0.001	0.062	1.002 (1.000-1.004)
Colonic polyp (patients with acromegaly)	0.950	0.633	0.134	2.585 (0.747-8.944)

OR: Odds Ratio; CI: Confidence Interval for Beta; IGF-1: Insulin-like growth factor-1.

(16). In our study also, PTC frequencies were 10.8%, 3.4% and 11.4% in the acromegalic, prolactinoma and CD patients, respectively. One study reported the PTC rate in prolactinomas as 5% (12), while only one case report so far has incidentally detected PTC in CD patients (22). In contrast, PTC is fairly common in patients with acromegaly (2-9, 17-21). However, these studies always compared one FPA type with the general population, and not among the different categories of FPA. The similar frequency of PTC seen among the different FPA groups in our study may reflect their com-

mon etiopathogenic mechanisms, including shared cytokines or growth factors (32-34). Another possibility is that the genetic and epigenetic factors that cause pituitary adenoma development may also be responsible for PTC. The common background of IR, metabolic syndrome, and DM may also act as secondary factors in these conditions. In order to reach more specific conclusions, further studies with a larger cohort are needed to evaluate these multiple factors.

Although it was difficult to compare the FPA groups in terms of PTC etiopathogenesis due to the small sample size, we compared the presence of NTD according to metabolic and clinical factors related to nodule formation in each group. As our study was designed retrospectively, the effects of factors such as smoking or body mass index on nodule formation could not be evaluated due to missing data in the registry files. Furthermore, the patients with NTD tended to be older in our cohort, consistent with previous reports stating that NTD frequency increases with age (1). On the other hand, pituitary adenoma size and TSH levels were similar between the groups. Although TSH levels have been associated with the development of thyroid nodules (35), the nodule development in acromegaly patients has been reported to be independent of TSH (36).

Glucose metabolism disorders, especially IR, are also related to both NTD and PTC development (37-41). In this study, pre-diabetes and DM were more common in patients with NTD. An increased NTD prevalence in the presence of these metabolic disorders may be a result of the interaction between the insulin pathway and the IGF-1 system, which leads to increased proliferation and differentiation of thyroid cells (42). Consistent with this hypothesis, increased NTD in patients with acromegaly was related with higher baseline IGF-1 levels in our series. In addition, Anil et al. (37) demonstrated that both thyroid volume and NTD frequencies were increased in diabetic patients and associated with the direct effects of IGF-1 and leptin-adiponectin on TSH secretion. In contrast, Ayturk et al. (43) showed that IR was effective in TSH secretion independent nodule formation in patients with metabolic syndrome. This finding is also in accordance with the results of Rezzonica et al. (38) who demonstrated the relationship between IR and NTD for the first time in iodine-sufficient regions. Although the mean HOMA-IR was similar for patients with or without nodules in our study, the results might have been different if only the patients who did not receive any IR treatment, such as metformin, were included in the study.

The higher baseline IGF-1 levels in acromegalic patients with NTD may be explained by the proliferative and antiapoptotic effects of IGF-1, as has been reported in previous studies (5, 10, 44). On the other hand, some studies have reported contradictory results (2, 4, 6, 45). In a recent study from Turkey, the incidence of thyroid nodules was reportedly increased in non-acromegalic patients with colonic polyps (46). In our study, a similar relationship was detected in acromegalic patients, which is probably related to increased proliferative factors affecting both the colon and thyroid epithelium. The most important indicator of this process is higher baseline IGF-1 levels in NTD patients. A positive relationship between intestinal crypt cell proliferation and elevated IGF-1 levels has been shown previously (47).

In a recent study, increased thyroid volume and NTD in prolactinoma patients were related to higher PRL levels (11). The PRL-receptors present on human thyroid cells may increase their proliferation, although this effect is more common in breast tissue and breast neoplasms (48, 49). We detected similar PRL levels in the prolactinoma patients with or without nodules. Further large-scale studies are needed in order to evaluate the effect of PRL levels on epithelial thyroid cells.

The baseline cortisol and ACTH levels were also similar between CD patients with or without NTD. Although no study supports our finding at present, Invitti et al. (14) reported higher NTD prevalence in patients with CD compared to adrenal Cushing syndrome. They also reported similar frequencies of NTD in patients with an active CD or those in remission, suggesting a lack of association with plasma cortisol levels, as supported by our results. Cytokines like IL-6 and growth factors that are secreted by the corticotroph cells during adenoma formation have also been implicated in thyroid nodule development (14).

In conclusion, the prevalence of NTD was higher in patients with acromegaly as expected. However, contrary to previous reports, the prevalence of PTC was similar between the different FPAs. Therefore, a close follow-up of NTD in prolactinoma and CD patients would be important for the early diagnosis of PTC. Further studies on larger cohorts are needed in order to assess the prevalence of PTC, and to specify the related risk factors.

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Authorship Contributions

Idea/Concept: Sema Çiftçi Doğanşen, Sema Yarman; Design: Sema Çiftçi Doğanşen, Gülşah Yenidünya Yalın; Control/Supervision: Sema Yarman; Data Collection and/or Processing: Seher Tanrıkulu, Sema Çiftçi Doğanşen; Analysis and/or Interpretation: Sema Çiftçi Doğanşen, Gülşah Yenidünya Yalın; Literature Review: Seher Tanrıkulu, Sema Çiftçi Doğanşen; Writing the Article: Gülşah Yenidünya Yalın, Sema Çiftçi Doğanşen; Critical Review: Sema Yarman; References and Fundings: Seher Tanrıkulu; Materials: Sema Çiftçi Doğanşen

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