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Differences in the Clinical Presentation of Patients with Adrenocorticotropic Hormone–Dependent Cushing's Syndrome

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Abstract

Objective: This study investigated the influence of ectopic and pituitary Cushing's syndrome, diagnosed by sampling the inferior petrosal sinus and cavernous sinus, on comorbidities and clinical complications.

Methods: Medical records of patients with Cushing's syndrome who presented to the Endocrinology, Metabolism, and Diabetes Clinic of İstanbul University-Cerrahpaşa, Faculty of Cerrahpaşa Medicine between 2010 and 2020 and underwent inferior petrosal and cavernous sinus sampling were reviewed. Sociodemographic data, clinical signs and symptoms, laboratory parameters, comorbidities, medical and surgical treatments applied, current disease status, and mortality data were recorded from all patients. Two groups were defined for the study: Cushing's disease and ectopic Cushing's syndrome. Data were compared between these 2 identified groups.

Results: This study was conducted with 106 patients. Ninety-four (88.7%) of the patients were women. The mean age at diagnosis was 52.1 ± 13.7 years. Twenty patients had ectopic Cushing's syndrome, and 86 patients had Cushing's disease. There were no statistical differences in age, sex, and follow-up time in the 2 groups. Basal cortisol level and cortisol level after a 2 mg low-dose dexamethasone suppression test were higher in ectopic Cushing's disease than in Cushing's disease (P = .04 and .05, respectively). Complications and comorbidities correlated with hypercortisolemia indicators. Body mass index was lower in ectopic Cushing's syndrome than in Cushing's disease (P < .001). There were no differences between groups in tests assessing glucose and lipid metabolism. Hypertension was present in 62.8% (n = 54) of patients with Cushing's disease. This rate was significantly higher than in ectopic Cushing's syndrome, as hypertension was significantly higher in patients with Cushing's disease than in patients with ectopic Cushing's syndrome (62.8% vs. 40%, P = .04). In terms of other comorbidities, the groups were similar. During the follow-up period, ectopic foci were detected in 3 patients with ectopic Cushing's syndrome, while no foci were found in the other patients. Forty-seven of 86 patients with pituitary Cushing's syndrome had adenoma on magnetic resonance imaging of the sella. All patients underwent hypophysectomy.

Conclusion: The clinical presentation in ectopic and pituitary Cushing's syndrome is determined by the cortisol level and the duration of the disease. In ectopic Cushing's syndrome, the acute or insidious onset of the disease affects the "clinical presentation," complications, and comorbidities depending on the underlying cause.

Keywords: ACTH-dependent Cushing's syndrome, hypercortisolemia, complication, comorbidity

Introduction

Cushing's syndrome is a serious endocrine disorder that causes chronic, autonomic, and excessive secretion of cortisol from the adrenal glands. The prevalence is estimated at 40 per million cases and the incidence at 0.7-2.4 cases per million.[1-3] Women are 3 times more likely to develop Cushing's syndrome than men.[1-4] Although Cushing's syndrome can occur at any age, it is more common in the third and fourth decades of life. In the vast majority of cases, Cushing's syndrome is caused by a pituitary adenoma, which causes excessive production of adrenocorticotropic hormone (ACTH) that stimulates the excessive secretion of cortisol from the adrenal cortex, referred to as Cushing's syndrome.[1-4] Adrenal overproduction of cortisol independent of ACTH due to adrenal adenoma or bilateral adrenal hyperplasia accounts for approximately 20% of cases of Cushing's syndrome.[1-4] Non-pituitary tumors secreting ACTH or very rarely corticotropin-releasing hormone (CRH) cause ectopic Cushing's syndrome in about 10% of cases.[1-4]

The clinical presentation of Cushing's syndrome consists of central obesity, weight gain, proximal myopathy, fatigue, purple striae, skin thinning, and easy bruising. Several comorbidities are associated with Cushing's syndrome and are responsible for the impaired quality of life and increased mortality.[1,2,4,5] These comorbidities include a specific form of metabolic syndrome characterized by hypertension, visceral obesity, impaired glucose metabolism, and dyslipidemia. This metabolic syndrome is associated with an increased incidence of cardiovascular disease as well as thromboembolism and hypokalemia.[1,2,4] Other clinical complications include myopathy, osteoporosis, skeletal fractures, and neuropsychiatric disorders such as cognitive impairment.[1,2,4] Another important complication of Cushing's syndrome is impaired immune function. It is associated with severe infections or sepsis during active disease, which is a direct consequence of increased cortisol secretion. Decreased cortisone levels during remission can lead

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to immune rebound, which can exacerbate underlying autoimmune diseases. Reproductive and sexual dysfunction are common in both men and women. Dermatologic manifestations also occur in both sexes, but specific dermatologic features (e.g., acne, hirsutism, and alopecia) are typically associated with the female sex.[1,2,4] Morbidity may increase in the long term, even after many years of remission, because it is present before diagnosis and disease.[6]

The onset of Cushing's syndrome is quieter has typical signs of Cushing's syndrome such as moon face, buffalo hump, and purple striae, and the disease may have a prolonged course. In patients with ectopic Cushing's syndrome, the onset of the disease is noisier, typical findings of Cushing's syndrome may be absent, patients have symptoms such as hypertension, hypokalemia, and hyperglycemia, and the disease duration is shorter.[7] In a meta-analysis, the time to diagnosis of Cushing's syndrome was found to be 38 months and 14 months for ectopic Cushing's syndrome. However, in patients diagnosed with ACTH-dependent Cushing's syndrome, it is often difficult to distinguish between Cushing's disease and ectopic Cushing's syndrome.[8]

Most studies reported on clinical complications of Cushing's syndrome do not provide high-quality evidence. In this study, the effects of pituitary and ectopic Cushing's syndrome on comorbidities and clinical complications were investigated.

Methods

This retrospective study was conducted at a single-center tertiary care university hospital. The study was approved by the Research Ethics Committee of İstanbul University-Cerrahpaşa, Faculty of Cerrahpaşa Medicine (Approval No: 167503, Date: December 24, 2020). Written informed consent was obtained from the patients who agreed to take part in the study. The study is in full compliance with the Declaration of Helsinki. Patient data were coded and stored anonymously.

Subjects and Methods

The medical records of patients diagnosed with Cushing's syndrome who were referred to the Endocrinology, Metabolism, and Diabetes Clinic İstanbul University-Cerrahpaşa, Faculty of Cerrahpaşa Medicine between 2010 and 2020 were scanned. Inclusion criteria were (1) definite diagnosis of Cushing's syndrome and (2) patients aged 18-65 years. The exclusion criteria were as follows: (1) patients with a diagnosis of exogenous and iatrogenic Cushing's syndrome, (2) ACTH-independent Cushing's syndrome, (3) patients excluded from regular follow-up and with incomplete medical records, and (4) patients with unknown etiology of Cushing's syndrome (flowchart in Figure 1). Patients who met these criteria were consecutively enrolled in the study.

Sociodemographic data, clinical signs and symptoms, laboratory parameters, comorbidities, applied medical and surgical treatments, current disease status, and mortality data were collected from all patients. Two groups were defined for the study: Cushing's disease and ectopic Cushing's syndrome. Data were compared between these 2 identified groups.

Diagnosis and Etiology of Cushing's Syndrome

The diagnosis of Cushing's syndrome was made by appropriate tests, such as the determination of freecortisol (UFC) in 24-hour urine, late-night plasma or salivary cortisol, and an overnight dexamethasone suppression test (DST) of 1 mg. Two positive tests in patients were considered hypercortisolism.[9] The classic 48-hour low-dose 2-mg DST (LDDST) test was used to confirm the diagnosis.[9] If the diagnosis was still controversial, a dexamethasone–CRH test was performed to make a final decision.[9] After the diagnosis of Cushing's syndrome, the cause was determined by measuring plasma ACTH levels. The diagnosis of adrenal Cushing's syndrome was made when plasma ACTH levels were less than 10 pg/mL.[9] ACTH-dependent Cushing's syndrome was assumed when the ACTH level was greater than 20 pg/mL.[9] A CRH stimulation test was performed when the plasma ACTH level was between 10 and 20 pg/mL. If the ACTH level rose above 20 pg/mL as a result of the test, ACTH-dependent Cushing's syndrome was diagnosed.[9] Magnetic resonance imaging (MRI) of the sella was performed to determine the etiology in patients with ACTH-dependent Cushing's syndrome. Patients with pituitary adenomas larger than 6 mm were diagnosed with Cushing's syndrome.[9] In the case of equivocal hormonal findings, suspicious pituitary imaging, and adenomas <6 mm, cavernous venous sinus-Sampling (CSS) or an inferior petrosal sinus sampling (IPSS) with CRH stimulation was used, to determine the central cause and provide an indication of lateralization.[9] Post-CRH stimulation ratios of >3.0 were defined as indicative of the pituitary source of ACTH. Lateralization ratios were calculated by comparing ACTH levels sampled simultaneously from the right and left cavernous sinus for each time point. The largest lateralization ratio >1.4 at any time point was used to predict the side of the pituitary adenoma.[9] When ectopic Cushing's syndrome was suspected, an examination with thoracic computed tomography (CT), abdominal CT/MRI, and somatostatin receptor scintigraphy was performed to determine the cause.

Statistical Analysis

Statistical analyzes were performed with the Statistical Package for the Social Sciences (SPSS) software (version 21.0) (IBM Corp., Armonk, NY, USA). Data were tested for normality using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± SD and/or median (interquartile range [IQR]). When comparing groups with normal data distribution, Student's *t*-test was used. Medians were compared using the Mann–Whitney *U* test and the Kruskal–Wallis test. Correlation between variables according to the distribution of the data was calculated using the Spearman and Pearson tests. Results were analyzed with a 95% CI. A *P* value < of .05 was considered statistically significant.

Sample Size

The required sample size was calculated as 106 for a 2-tailed *t*-test with a significance level of 5% to achieve a power of 81%.

Results

Patient Characteristics

This study was conducted with 106 patients. Ninety-four (88.7%) of the patients were women. Twenty patients were diagnosed with ectopic Cushing's syndrome and 86 with Cushing's disease (18% and 72%, respectively). The mean age of patients at diagnosis was 52.1 ± 13.7 years. Twenty patients had ectopic Cushing's disease and 86 patients had Cushing's disease. There was no significant difference between groups in age, sex, and follow-up time ($P > .05$ for all parameters). The general characteristics of the patients and symptoms at presentation are shown in Table 1. Weight gain occurred in 70 (66%) of patients and was the most common symptom. Weight loss was significantly higher in patients with ectopic Cushing's syndrome.

Comparison of Laboratory Parameters and Comorbidities According to Causes of Hypercortisolemia

Table 2 provides a comparison of the laboratory results of hypercortisolemia, glucose panel, and lipid panel between the groups. Basal cortisol and cortisol levels by LDDST were significantly

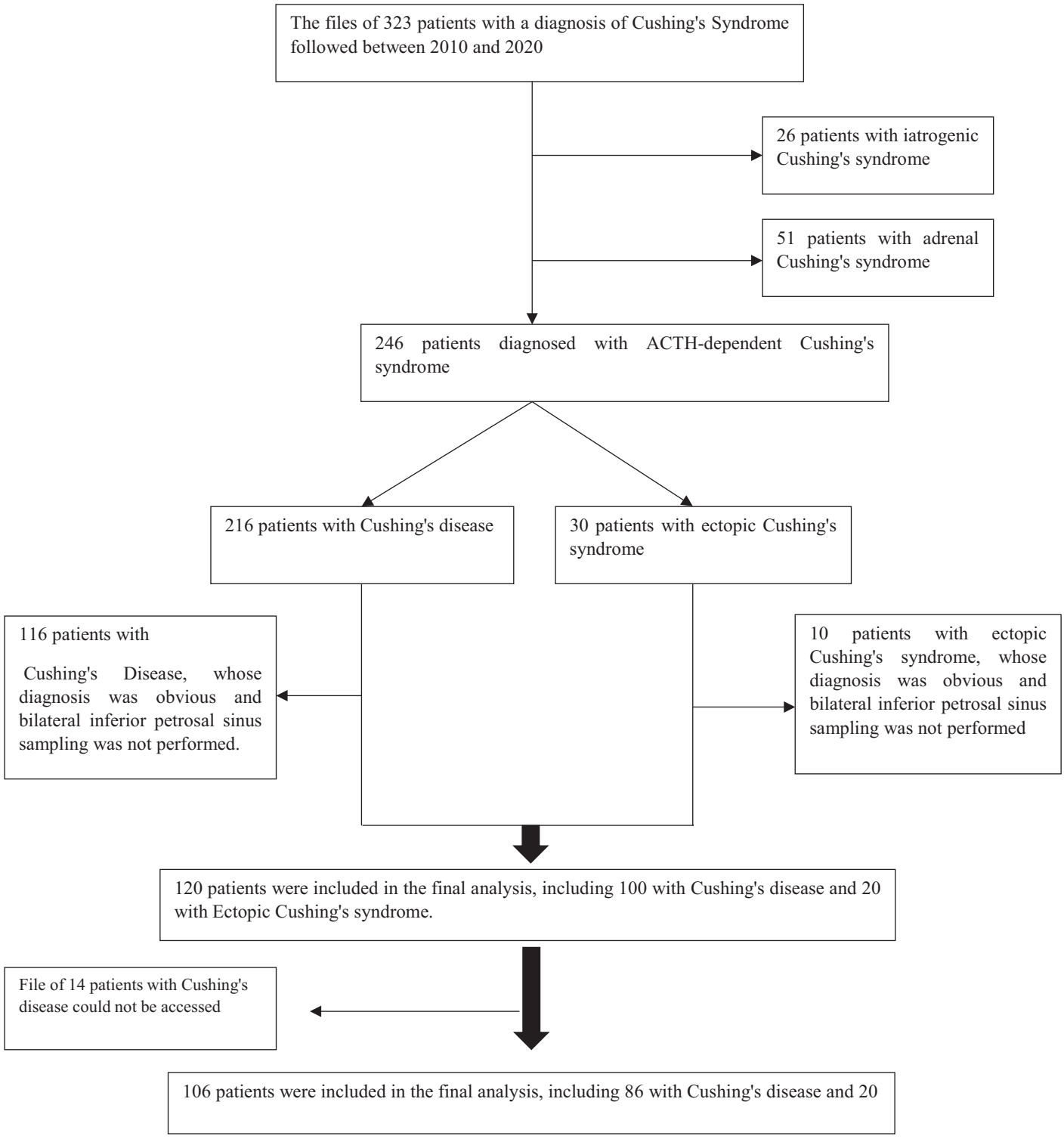

Figure 1. Study flowchart.

higher in the ectopic Cushing's syndrome than in the pituitary Cushing's syndrome group. Salivary and urinary cortisol, basal ACTH, and cortisol levels after 1 mg DST were not statistically different between groups. The values of parameters assessing glucose and lipid metabolism were similar in both groups.

The comorbidities of the 2 groups are shown in Table 3. Hypertension was present in 62.8% (n = 54) of patients with pituitary Cushing's syndrome. This rate was significantly higher than in ectopic Cushing's syndrome (P = .04). It was similar for other comorbidities.

Correlation Analysis

The relationship between hypercortisolemia indicators (basal cortisol, basal ACTH, late-night salivary cortisol, 24-hour UFC, 1 mg DST, and LDDST) and complications and comorbidities is shown in Table 4.

Table 1. General Characteristics of the Patients and Symptoms at Presentation

	Ectopic Cushing's Syndrome (n = 20)	Cushing's Disease (n = 86)	*P*
Sex, female, n (%)	18 (90)	76 (88)	.8
Age of diagnosis, years, mean ± SD	45 ± 12	44 ± 14	.4
Disease duration, month, median (IQR)	50 (24-60)	60 (27-96)	0.6
BMI (kg/m²)*	22 ± 3.3	30 ± 3.6	**<.001**
Weight gain, n (%)	13 (65)	57 (66)	.6
Weight loss, n (%)	4 (20)	2 (2.3)	**.003**
Hirsutism, n (%)	5 (25)	16 (18.6)	.35
Menstrual changes, n (%)	4 (20)	8 (9.3)	.09
Moon face, n (%)	7 (35)	12 (14)	.02
Buffalo hump, n (%)	4 (20)	20 (23)	.8
Purplish striae, n (%)	3 (15)	18 (21)	.6
Death n (%)	2 (10)	6 (7)	.6

P < .05 was considered statistically significant.
* BMI, body mass index; IQR, interquartile range.Ectopic
Bold: Basal cortisol levels were statistically higher in ectopic Cushing's syndrome than in Cushing's disease

Table 3. Comorbidities in the Follow-Up of Patients

	Ectopic Cushing's Syndrome (n = 20)	Cushing's Disease (n = 86)	*P*
Hypertension, n (%)*	8 (40)	54 (62.8)	**.04**
Diabetes mellitus, n (%)	8 (40)	37 (43)	.6
Cardiovascular disease, n (%)	1 (5)	8 (9.3)	.4
Proximal myopathy, n (%)	7 (35)	16 (18.6)	.1
Osteoporosis, n (%)	3 (15)	13 (15.1)	.8
Thromboembolism, n (%)	0 (0)	6 (7)	.2

P < .05 was considered statistically significant.
Bold: The prevalence of hypertension was statistically lower in ectopic Cushing's syndrome than in Cushing's disease.

Treatment and Follow-Up Outcomes

During the follow-up period of 20 patients with ectopic Cushing's syndrome, a disease focus was detected in 3 of them. One of them was an endometrial carcinoma that was in remission after surgery, 1 was a small cell lung carcinoma that died, and the other was a bronchial carcinoid that was operated on and was in remission. In other patients, the focus could not be detected. Bilateral adrenalectomy was performed in 7 patients with catastrophic disease. Because 9 patients had milder symptoms, they are being continued on drug treatment with dopamine agonists and ketoconazole. During the follow-up period, 2 patients died, one because of lung carcinoma and the other because of a cerebrovascular event.

Table 2. Laboratory Parameters of the Patients at Admission

	Ectopic Cushing's Syndrome (n = 20)	Cushing's Disease (n = 86)	*P*
Basal ACTH, NV 0-46 ng/L, mean ± SD	61.6 ± 50.8	48.2 ± 36.2	.3
Basal cortisol, NV 6.2-19.4 µg/dL, mean ± SD	30.9 ± 14.6	24.2 ± 12.5	**.04**
1-mg DST,* NV <1.8 µg/dL, mean ± SD	16.2 ± 14.9	10.5 ± 9	.08
Salivary cortisol, NV <0.2 µg/dL, mean ± SD	3.9 ± 2.9	3.1 ± 2	.2
24-hour UFC, ×ULN, mean ± SD	3.3 ± 2.7	4.4 ± 3	.3
LDDST,** NV <1.8 µg/dL, median (IQR)	9.8 (3.6-19.7)	5.2 (2.7-10.9)	**.05**
Plasma glucose, NV 74-109 mg/dL, median (IQR)	99 (76-118)	99 (84-119)	.2
HbA1c, NV 4.8%-6%, median (IQR)	6.3 (5.2-6.8)	6.3 (5.5-7)	.3
Total cholesterol, NV 50-200 mg/dL, mean ± SD	197.9 ± 59.2	199.4 ± 41.3	.5
Triglyceride, NV <200 mg/dL, mean ± SD	162.9 ± 97.2	144 ± 85.5	.6
LDL cholesterol, NV <140 mg/dL, mean ± SD	136.9 ± 38.1	130.5 ± 35.4	.5
HDL cholesterol, NV >60 mg/dL, mean ± SD	53.9 ± 14.8	52.1 ± 14.3	.6

P < .05 was considered statistically significant.
*Cortisol levels after late night 1 mg dexamethasone.
**Cortisol level measured after 48 hours given 0.5 mg of dexamethasone every 6 hours.
Bold: Basal cortisol levels were statistically higher in ectopic Cushing's syndrome than in Cushing's disease
ACTH, adrenocorticotropic hormone; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; LDDST, low-dose dexamethasone suppression test; LDL, low-density lipoprotein; NV, normal values; UFC, urine-free cortisol; ULN, upper limit of normal.

Table 4. Univariate Correlation Analysis

Night salivary cortisol	*Hirsutism r* = **0.451** *P* = **.05**	**1 mg DST** *Buffalo hump r* = **0.326** *P* = **.002**
	Moon face r = 0.532 *P* = .023	*Hirsutism r* = 0.345 *P* = .001
		Moon face r = 0.454 *P* < .001
		Menstrual changes r = 0.238 *P* = .03
		Purple striae r = 0.221 *P* = .04
Basal ACTH	*Hirsutism r* = 0.381 *P* = .001	
	Moon face r = 0.411 *P* < .001	
	Death r = 0.294 *P* = .008	
	Purple striae r = 0.286 *P* = .012	
	Osteoporosis r = 0.272 *P* = .015	
24-Hour UFC	*Hirsutism r* = 0.336 *P* = .03	
	Osteoporosis r = 0.301 *P* = .05	
LDDST	*Buffalo hump r* = 0.252 *P* = .03	
	Gain weight r = 0.274 *P* = .017	
	Hirsutism r = 0.414 *P* < .001	
	Menstrual changes r = *r* = 0.254 *P* = .037	
	Moon face r = 0.455 *P* < .001	

P < .05 was considered statistically significant.
ACTH, adrenocorticotropic hormone; DST, dexamethasone suppression test; LDDST, low-dose dexamethasone suppression test; UFC, urine-free cortisol.

Forty-seven of 86 patients with pituitary Cushing's syndrome had an adenoma on MRI of the sella. The diagnosis was made in all of them by sampling from the cavernous sinus or inferior petrosal sinus. All patients underwent adenomectomy. Seventeen patients experienced remission after surgery. Bilateral adrenalectomy and gamma-knife radiosurgery were performed in 7 and 11 patients, respectively, who were not in remission after surgery. Fifty-eight patients continued to receive drug treatment (34 patients with pasireotide, 3 patients with ketoconazole, 10 patients with cabergoline, and 11 patients with metyrapone combination). During the follow-up period, 5 patients died because of comorbidities of Cushing's syndrome. Three patients died of myocardial infarction, and 2 patients died of cerebrovascular accident. One patient died of breast cancer.

Seventy-two patients were in remission. Fourteen patients were not in remission because 4 patients did not respond to treatment with pasireotide, treatment with metyrapone was initiated, and the metyrapone dose was increased in 10 patients. Appropriate medical treatments are provided for the patients' comorbidities.

Discussion

Our study examined difficult cases in which the origin of Cushing's syndrome could not be determined to be pituitary or ectopic at baseline.

Although cortisol levels were higher in ectopic Cushing's syndrome than in pituitary Cushing's syndrome, no significant difference was found between complications and comorbidities, except for weight loss and the occurrence of hypertension. Complications and comorbidities correlated with indicators of hypercortisolemia.

The clinical presentation of Cushing's syndrome depends in part on cortisol excess and duration of exposure. In severe hypercortisolemia, the signs and symptoms are obvious. In particular, proximal muscle weakness, increase of fat in the abdomen, trunk, and face, weakening of the extremities, and broad purple lines indicate marked hypercortisolism.[10,11] The results of our study are also consistent with the literature: biochemical hypercortisolemia indicators were correlated with complications and comorbidities. In this study, it was found that cortisol levels of patients with ectopic Cushing's syndrome were higher than those of patients with pituitary Cushing's syndrome.

However, no significant difference was found in weight gain, hirsutism, menstrual changes, buffalo hump, purple lines, and moon face between the 2 groups. However, the results of the study may be due to the fact that we were unable to determine the exact timing of exposure to hypercortisolemia.

In the review by Valassi et al, 1045 cases of Cushing's disease and 89 cases of ectopic Cushing's syndrome were studied. The most common symptoms were weight gain, hyperpigmentation, skin changes, and myopathy.[12] Patients with ectopic Cushing's syndrome had diabetes mellitus, myopathy, hirsutism, and vertebral fractures more frequently compared with Cushing's disease.[12] In our study, the symptoms and findings of the 2 endogenous Cushing's syndromes were similar except for weight loss, hypertension, and body mass index (BMI). However, we believe that the evaluation will be healthier if we increase the number of observations. Weight gain, hypertension, and diabetes were the most common findings in 2 endogenous Cushing syndromes. In addition, proximal myopathy and moon face in ectopic Cushing's syndrome and buffalo hump, purple streak, hirsutism, proximal

myopathy, and osteoporosis in Cushing's syndrome were common findings. The diagnosis and origin of ectopic Cushing's syndrome are difficult to determine. Symptoms appear months before diagnosis, with a median time to diagnosis of up to 2 years.[13,14] In some patients, the tumor focus cannot be found.[15,16] It is difficult to detect an ectopic source with CT and MRI.[16] 111-indium-labeled octreotide scintigraphy (111In-OCT) has been successful in detecting ectopic sources because the majority of bronchial carcinoid tumors express receptors for somatostatin.[17] In this study, the source was determined in 3 of 20 cases of ectopic Cushing's syndrome. In our cases in which ectopic ACTH was secreted, a lung carcinoid tumor was detected by somatostatin receptor scintigraphy, endometrial carcinoma by abdominal MRI, and small cell lung carcinoma by chest examination CT. In 17 of our cases, the cause could not be found during the follow-up period (median 50 months).

Proopiomelanocorticotropin (POMC), the precursor of ACTH, is secreted more in ectopic Cushing's syndrome.[18] It affects energy intake due to the appetite-suppressing effect of the POMC molecule. In this study, the BMI of ectopic patients was found to be lower. Ectopic Cushing's syndrome can be acute or chronic.[19] The acute syndrome is manifested by the rapid onset of hypertension, prediabetes, fatigue, edema, hypokalemia, weakness, anorexia, and weight loss. In most cases, there is no typical Cushing's phenotype. The most common source of ectopic corticotropy is small-cell lung carcinoma.[15] The chronic syndrome often resembles pituitary-dependent hypercortisolism and presents with a plethora of trunk adiposity, buffalo hump, and purplish streaks.[20] In this study, cases of endometrial and lung cancer showed proximal myopathy and weight loss, and cases of carcinoid tumors showed purple stripes, central obesity, and proximal myopathy.

The pathophysiology of arterial hypertension in patients with Cushing's syndrome is multifactorial and not fully understood. Arterial hypertension in patients appears to be the result of both hypercortisolism and activation of the renin–angiotensin–aldosterone system.[10,21-26] These complex processes cause secondary endothelial dysfunction,[27-30] and developing atherosclerotic plaques lead to an increase in carotid intima-media thickness at a young age.[28,31,32] Therefore, increased arterial stiffness and abnormal vasoconstriction are involved in the pathophysiology of arterial hypertension in this group of patients.[30] One of the most common complications of long-term excessive glucocorticoid exposure is arterial hypertension, which develops in more than 70% of patients with Cushing's syndrome and is an important risk factor for mortality in this patient group.[6,31,33,34] In this study, cortisol levels were higher in patients with ectopic Cushing's syndrome. However, hypertension was observed more frequently in patients with pituitary Cushing's syndrome. The average age of the 2 groups was similar. We do not know how long the patients were exposed to hypercortisolemia. In addition, we did not have information on the history of essential hypertension. In addition, we did not know whether the patients had essential hypertension.

Endothelial dysfunction and changes in hemostatic parameters increase the risk of thrombotic events. Arterial and venous thrombotic events lead to morbidity and mortality. Deaths from cardiovascular and pulmonary embolism account for most deaths. Cushing's syndrome leads to an increased risk of hypertension, dyslipidemia, diabetes, osteoporosis, cardiovascular, and thromboembolic disease.[35] Several studies have found an increased mortality rate, mostly due to vascular diseases such as myocardial infarction and stroke, infectious diseases, and venous or arterial thromboembolism.[36] Thrombotic events occur in approximately 1 in 5 patients with Cushing's syndrome, with arterial and venous events occurring equally.[37] In our study, the most common comorbidities in both groups were hypertension and diabetes. The incidence of cardiovascular events was 10%, and complications from thromboembolism were 7% in the overall series. Of the deaths, 37.5% were due to cardiovascular events, 37.5% to cerebrovascular events, and 25% to malignancies.

Conclusion

Clinical presentation of endogenous Cushing's syndrome: in Cushing's disease and adrenal Cushing's syndrome, cortisol levels and duration of disease are critical. In ectopic Cushing's syndrome, the acute or insidious onset of the disease affects complications and comorbidities depending on the underlying cause.

Limitations

The present study has several limitations. The data on time from symptom onset to diagnosis were inconclusive. This was a single-center study with a limited number of patients. The model might behave differently with more data and patients from multiple centers.

Data Statement: All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author. The data used and analyzed during the current scoping review are available from the corresponding author upon reasonable request.

Ethics Committee Approval: The study was approved by the local Institutional Review Board, the Ethics Committee of the Cerrahpaşa Faculty of Medicine, (Approval No: 167503, Date: December 24, 2020) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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