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Pituitary Corticotroph Microadenomas Versus Macroadenomas Causing Cushing's Disease

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Abstract: *Purpose:* Pituitary corticotroph macroadenomas are accused for a minority of cases of Cushing's disease but their actual prevalence is believed to be underestimated. Further, clinical and biochemical manifestations of corticotroph macroadenomas and microadenomas differ widely and only small numbers of patients have been included for analysis in previous studies. We aimed to analyze and compare the clinical characteristics and biochemical features of patients with corticotroph macroadenomas and microadenomas causing Cushing's disease.

Methods: We included 107 patients with Cushing's disease (67 microadenomas and 40 macroadenomas) in this analysis. Clinical characteristics, biochemical analysis of hypercortisolism, pituitary imaging findings, treatment modalities, remission as well as recurrence rates were recorded.

Results: Mean age of patients at diagnosis was 46.5 ± 11.4 years for macroadenomas and 37.3 ± 12.1 years for microadenomas ($p < 0.001$). Gender distribution was equal in macroadenoma patients whereas female predominance was apparent in microadenoma patients ($p = 0.001$). Compared to macroadenoma patients, clinical evidence of hypercortisolism was more pronounced with microadenomas. Although the presentation of clinical manifestations was different, biochemical analysis of hypercortisolism including basal cortisol, ACTH, 24-hour urinary cortisol levels, and responsiveness to low-dose dexamethasone suppression were similar between the groups. Suppressability of serum cortisol after high-dose dexamethasone was lower in macroadenomas but did not reach significance ($p = 0.074$). Remission rates after initial pituitary surgery (67.5 % vs 82.8 %) and recurrence rates in patients followed beyond 6 months were similar between groups.

Cavernous sinus invasion was found to be a negative predictor of remission.

Conclusion: Patients with corticotroph macroadenomas and microadenomas share similar biochemical evidence of hypercortisolism, remission and recurrence rates but presenting clinical manifestations are different. Cavernous sinus invasion is a negative predictor of remission.

Key words: Cushing's disease, corticotroph macroadenoma, corticotroph microadenoma, cavernous sinus invasion

Kurzfassung: Kortikotrope Hypophysen-Makroadenome vs. Mikroadenome als Ursache des Morbus Cushing. *Ziel:* Kortikotrope Hypophysen-Makroadenome werden für eine geringe Zahl von Fällen des Cushing-Syndroms verantwortlich gemacht. Man geht jedoch davon aus, dass ihre genaue Prävalenz unterschätzt wird. Des Weiteren fallen die klinischen und biochemischen Manifestationen kortikotroper Makro- und Mikroadenome sehr unterschiedlich aus und in bisherigen Studien wurde nur eine geringe Anzahl von Patienten eingeschlossen. In dieser Arbeit analysieren und vergleichen wir die klinischen Charakteristika und biochemischen Eigenschaften von Patienten mit kortikotropen Makro- und Mikroadenomen, die Morbus Cushing verursachen.

Methoden: Wir schlossen 107 Patienten mit M. Cushing ein (67 Mikroadenome, 40 Makroadenome). Klinische Charakteristika, biochemische Analysen des Hyperkortisolismus, Ergebnisse des Hypophysen-Imagings, Behandlungsmodalitäten sowie Raten für Remission und Wiederauftreten wurden erfasst.

Ergebnisse: Das Durchschnittsalter der Patienten lag bei $46,5 \pm 11,4$ Jahren für Makroadenome und $37,3 \pm 12,1$ Jahre für Mikroadenome ($p < 0,001$). Die Geschlechterverteilung war bei den Makroadenomen gleich, während bei den Mikroadenomen eine Vorherrschen der Frauen offensichtlich war ($p = 0,001$). Verglichen mit den Makroadenomen war die klinische Evidenz des Hyperkortisolismus bei den Mikroadenomen stärker ausgeprägt. Obwohl die klinischen Manifestationen differierten, waren die biochemische Analyse des Hyperkortisolismus (inklusive Basalkortisol, ACTH, 24-Stunden-Harnkortisol-Level) und Ansprechen auf eine niedrig dosierte Dexamethason-Suppression zwischen den Gruppen ähnlich. Die Unterdrückbarkeit des Serumkortisols nach Gabe von hochdosiertem Dexamethason war für Makroadenome niedriger, erreichte aber keine Signifikanz ($p = 0,074$). Die Remissionsraten nach dem ersten hypophysenchirurgischen Eingriff (67,5 vs. 82,8 %) sowie die Rezidivraten bei Patienten, die länger als 6 Monate nachverfolgt wurden, waren bei beiden Gruppen vergleichbar. Ein Einwachsen in den Sinus cavernosus war ein negativer Prädiktor für Remission.

Schlussfolgerung: Patienten mit kortikotropen Makro- und Mikroadenomen haben ähnliche laborchemische Veränderungen sowie Remissions- und Rezidivraten. Unterschiede gibt es jedoch bei der klinischen Präsentation. Ein Einwachsen des Tumors in den Sinus cavernosus ist ein negativer Prädiktor für Remission. **J Klin Endokrinol Stoffw 2014; 7 (3): 96–101.**

Schlüsselwörter: Morbus Cushing, kortikotropes Makroadenom, kortikotropes Mikroadenom, Sinus-cavernosus-Invasion

■ Introduction

Cushing's disease is characterised by endogenous glucocorticoid excess resulting from ACTH-secreting pituitary corticotroph adenoma, < 10 mm in diameter in most of the cases [1]. Pituitary corticotroph macroadenomas were initially accused for a minority of the cases but their rates have been reported to range between 4–10 % and 50 % [2–5].

Different clinical and biochemical characteristics of corticotroph macroadenomas and corticotroph microadenomas have

been reported so far. However, consistence in clinical and biochemical evidence of hypercortisolism, even in the prevalence of macroadenomas, could not be provided. Several reports defined corticotroph macroadenomas to be associated with indolent disease [6] while others noted that evidence of hypercortisolism was more prominent in macroadenomas [5].

Due to the rarity of the reports in this field, we aimed to analyze and compare the clinical characteristics, biochemical levels of hypercortisolism, remission rates, and recurrence rates of patients with corticotroph macroadenomas and microadenomas in a tertiary referral hospital.

■ Subjects and Methods

Patients

The dataset contains 107 patients with pituitary ACTH-secreting adenomas diagnosed between January 2000 and December 2011. Medical records of the patients were reviewed retrospectively for signs and symptoms, anthropo-

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metric measurements, biochemical analysis, imaging findings of pituitary, treatment modalities, and remission rates. Patients were classified into 2 groups according to the maximum diameter of the tumour described with magnetic resonance imaging (MRI). Tumours with a maximum diameter ≤ 10 mm were defined as microadenoma and > 10 mm as macroadenoma. Invisible adenomas were included in the microadenoma group.

Endocrine Evaluation

The diagnosis of Cushing's disease (CD) was based on clinical signs and symptoms, biochemical hypercortisolism, inferior petrosal sinus sampling (IPSS) results, and histopathologic examination. Moreover, in the evaluation of hypercortisolism, currently accepted criteria were utilized [1]. An overnight low-dose dexamethasone suppression test (LDDST, 2 mg) and 24-hr urinary free cortisol (UFC) excretion were performed to detect hypercortisolism. Early-morning serum cortisol and ACTH were also determined. An overnight 8-mg dexamethasone suppression test (HDDST) was performed in 64 patients and suppression of serum cortisol $> 50\%$ of the baseline value was accepted as "responsive". Furthermore, in determining the pituitary origin of the disease, normal/high ACTH concentrations, responsive 8-mg DST, central gradient in IPSS along with pituitary MRI findings were used as the decision basis.

Treatment Modalities

Of the 107 patients, one patient refused surgery, one patient preferred another centre for surgery, and one patient died before the scheduled time of the surgery. Of the remaining 104 patients, 2 had transcranial surgery and 102 had transphenoidal surgery, initially. For all cases, the surgeons' reports about the resectability of the tumour and about the success of the resection during the operation were recorded. Three patients had immediate re-surgeries after failure of initial surgery and 2 of them were regarded as cured later on. In addition, other than the need for immediate second surgery, 20 patients required additional surgeries for persistent or relapsed disease. On the other hand, 8 patients received radiotherapy, either stereotactic Cyberknife surgery ($n = 6$) or conventional radiotherapy ($n = 2$), while none of the patients were treated medically.

Remission and Relapse

Postoperative remission or cure of CD was defined as improvement in clinical signs and symptoms of hypercortisolism, requirement of exogenous glucocorticoids for the signs and symptoms of adrenal insufficiency, and biochemical recovery from hypercortisolism. In general, morning serum cortisol levels < 5.0 $\mu\text{g/dl}$ within 2 weeks after surgery were accepted as biochemical recovery from hypercortisolism. Patients who had morning cortisol levels > 5.0 $\mu\text{g/dl}$ were tested up to 6 weeks after surgery to detect the delayed decline in cortisol levels due to possible transient adrenal autonomy. Requirement of exogenous glucocorticoids, suppression of

serum cortisol < 2.0 $\mu\text{g/dl}$ after low-dose DST, and normal 24-hr UFC in this period were also defined as remission. Relapse, on the other hand, was defined as the recurrence of clinical and biochemical hypercortisolism and it was determined in patients with a follow-up period of > 6 months. Overall, 47 patients were eligible for evaluation of relapse state.

Statistical Analysis

Analysis of data was conducted using SPSS 18.0 (Statistical Package for Social Sciences, SPSS Inc, Chicago, IL, US). The distribution of numerical variables was assessed using the Kolmogorov-Smirnov test. Numerical variables were compared between groups by Student's T Test and Mann-Whitney U Test while the Chi-square test (Pearson Chi-square, Continuity Correction, Fisher's Exact Test) was used for comparing categorical variables. Stepwise multiple logistic regression was performed to identify factors predictive of remission and recurrence. Data were expressed as mean \pm SD or median (minimum/maximum) when appropriate. $P < 0.05$ was considered significant.

■ Results

Clinical and Biochemical Patient Characteristics

The study included 35 male (32.7 %) and 72 female (67.3 %) patients with Cushing's disease. Of the 107 patients, 67 (62.6 %) had a microadenoma and 40 (37.4 %) had a macroadenoma. Mean maximum diameter of microadenomas was 5.4 ± 2.3 mm and 22.6 ± 10.1 mm for macroadenomas. Three patients who did not undergo pituitary surgery had microadenomas. Among the 2 patient groups the presence of diabetes, osteoporosis, hypertension, dislipidaemia, and myopathy was found to be similar. There was a significant gender difference between groups with a female predominance in the microadenoma group ($p = 0.001$). In terms of age, patients in the macroadenoma group were on average 10 years older ($p < 0.001$). Table 1 presents the clinical and biochemical features of the patients. Body Mass Index (BMI) was comparable between the groups, whereas central distribution of body fat indicated by the presence of central obesity, buffalo hump, and supraclavicular fat was significantly higher in

Table 1. Comparison of clinical and biochemical features of patients with Cushing's disease caused by corticotroph microadenomas and macroadenomas before pituitary surgery.

	Microadenoma	Macroadenoma	p
Gender (male : female)	14:53	21:19	0.001
Age (years)	37.3 ± 12.1	46.5 ± 11.4	< 0.001
Body Mass Index (kg/m^2)	30.7 ± 6.2	31.5 ± 8.0	0.559
Fasting glucose (mg/dl)	111.1 ± 4.6	113.2 ± 54.9	0.826
K (mEq/l)	4.18 ± 0.60	4.21 ± 0.77	0.813
Total cholesterol (mg/dl)	208.5 ± 37.8	225.9 ± 37.9	0.191
Triglycerides (mg/dl)	169.0 ± 71.9	165.3 ± 70.2	0.886
HDL-C (mg/dl)	53.4 ± 16.8	52.9 ± 15.2	0.993
LDL-C (mg/dl)	119.6 ± 35.0	143.7 ± 31.8	0.050
Leucocytes ($10^3/\text{mm}^3$)	10.1 ± 2.9	8.9 ± 3.1	0.059
Neutrophils (%)	69.2 ± 12.8	63.4 ± 10.9	0.021
Lymphocytes (%)	20.4 ± 8.1	25.2 ± 7.8	0.005

Values are expressed as mean \pm SD.

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol

microadenoma patients ($p < 0.001$ for each of the 3 features). Furthermore, biochemical analysis including electrolytes, lipid profile, and fasting glucose levels did not differ between the groups. Neutrophil counts were significantly higher ($p = 0.021$) and lymphocyte counts significantly lower in microadenoma patients ($p = 0.005$) while the difference in total leucocyte counts was not statistically significant ($p = 0.059$).

Signs and symptoms of the patients with Cushing’s disease are given in Table 2. The figures show that patients with macroadenomas often present symptoms of intracranial mass effect such as headache and visual problems ($p < 0.001$). Moreover, moon face, plethora, purple stria, and hirsutism were more prevalent in the microadenoma group and other signs and symptoms

such as easy bruising, muscle weakness, acne, or mood changes were also frequently experienced; however, statistically the latter group of signs and symptoms did not reach significance.

According to imaging findings, macroadenomas were – as expected – more invasive than microadenomas. Pituitary MRI demonstrated cavernous sinus invasion in 11 macroadenoma patients and one microadenoma patient. Suprasellar extension of the tumour was present in 13 macroadenoma patients and 3 microadenoma patients (each $p < 0.001$).

Endocrine Evaluation

Biochemical values of hypercortisolism are shown in Table 3. Basal serum cortisol, ACTH, and cortisol-to-ACTH ratios

were found to be similar. In the sample, nearly all patients had non-suppressible cortisol levels after LDDST. One patient with a macroadenoma and one with a microadenoma were responsive to LDDST, and both of them had elevated urinary cortisol levels and high ACTH levels. Cortisol suppression $> 50\%$ after HDDST was present in 90.2 % of microadenoma and 69.2 % of macroadenoma patients (ns; $p = 0.074$) while UFC levels were not different between the groups ($p = 0.401$). The results in the table show that postoperative nadir serum cortisol levels and cortisol-to-ACTH ratios were not different. However, nadir ACTH levels during the first 14 days following surgery were higher in the macroadenoma group ($p = 0.024$). Preoperative and postoperative nadir cortisol and ACTH levels are also shown in Figure 1.

Treatment, Histopathological Evaluation, and Remission

Of the 104 patients who underwent pituitary surgery at our centre, 57 patients had remission based on the measurement of morning cortisol levels $< 5 \mu\text{g/dl}$ within 2 weeks after surgery and 23 patients had remission according to the evaluation between 2 and 6 weeks. Accordingly, a total of 80 patients had remission in the postoperative period. Six patients were lost to follow-up after early postoperative evaluation and 18 patients were not in remission after initial surgery. 53 patients (82.8 %) with a microadenoma and 27 patients (67.5 %) with a macroadenoma were in remission after initial surgery (Figure 2). No significant difference was detected in remission rates between the groups ($p = 0.191$).

Among possible surgery types, adenomectomy was clearly preferred (94.2 %).

Table 2. Signs and symptoms of the patients with Cushing’s disease caused by corticotroph macroadenomas and microadenomas.

Complaint	All patients (%)	Microadenomas (%)	Macroadenomas (%)	p*
Headache	43.0	32.8	60.0	0.011
Visual problems	23.4	11.9	42.5	0.001
Moon face	61.7	80.6	30.0	< 0.001
Plethora	59.6	80.6	21.6	< 0.001
Weight gain	64.5	82.1	37.5	< 0.001
Central obesity	73.8	91.0	45.0	< 0.001
Buffalo hump	57.0	73.1	30.0	< 0.001
Supraclavicular fat	60.7	79.1	30.0	< 0.001
Purple stria	45.3	60.6	20.0	< 0.001
Hirsutism	46.7	62.7	20.0	< 0.001
Galactorrhoea	15.7	9.4	26.3	0.046
Oligo-/amenorrhoea	53.5	53.8	52.6	1.00
Decreased libido	43.8	42.4	46.2	0.866
Impotence	32.4	21.4	40.0	0.295
Bruising	26.7	33.8	15.0	0.058
Muscle weakness	16.2	21.5	7.5	0.104
Acne	14.0	19.4	5.0	0.074
Hyperpigmentation	17.8	14.9	22.5	0.465
Mood changes	29.5	35.4	20.0	0.145

*Microadenomas vs macroadenomas

Table 3. Comparison of biochemical values of hypercortisolism in patients with Cushing’s disease caused by corticotroph microadenomas and macroadenomas.

	Microadenoma	Macroadenoma	p
Basal ACTH (ng/l)	58.7 (11.3–687)	69.1 (10.7–1250)	0.240
Basal serum cortisol ($\mu\text{g/dl}$)	24.9 \pm 13.4	20.2 \pm 11.3	0.064
Cortisol-ACTH ratio	0.38 (0.09–2.45)	0.27 (0.03–4.41)	0.453
Urinary cortisol ($\mu\text{g}/24$ hours)	251 (50–2408)	261 (99–470)	0.401
Responsive HDDST (51/13)	46 (90.2 %)	9 (69.2 %)	0.074
Postoperative nadir ACTH	14.2 (3–85.4)	25.6 (1.2–102)	0.024
Postoperative nadir serum cortisol ($\mu\text{g/dl}$)	3.7 (1–63.1)	6.5 (1.15–41.5)	0.983
Postoperative nadir cortisol-ACTH ratio	0.27 (0.04–2.42)	0.24 (0.02–2.25)	0.769

Values are expressed as mean \pm SD or median (range) when appropriate. HDDST: high-dose dexamethasone suppression test

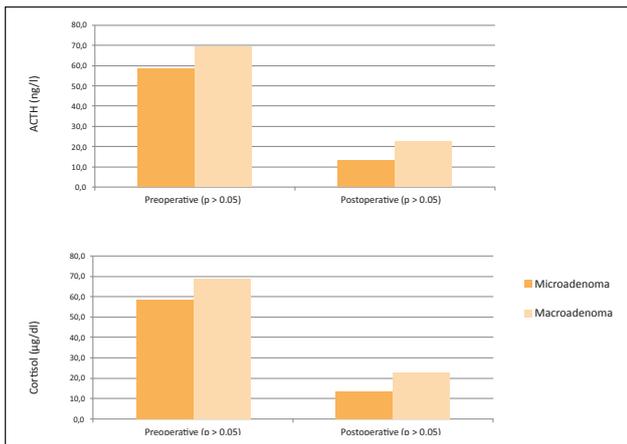


Figure 1. Preoperative and postoperative ACTH and cortisol levels in microadenoma and macroadenoma patients.
* Postoperative ACTH and cortisol levels are nadir levels within a postoperative period of 2 weeks. Median values are presented for variables.

Only 6 microadenoma patients (5 hemihypophysectomy, one total hypophysectomy) were operated by hypophysectomy and half of them had remission after surgery. Surgeons reported that the tumour was easily resected in 67.2 % of microadenoma and in 52.5 % of macroadenoma patients ($p = 0.045$). However, reports of neurosurgeons about the success of the operation were not found to be predictive on the postsurgical outcome in multiple regression analysis.

Histopathological examination of the resected specimen revealed no lesion in 12 microadenoma patients; however, 7 of them had remission after surgery. Five microadenoma patients and 4 macroadenoma patients showed weak GH staining while 4 patients in the microadenoma and macroadenoma groups each had weak prolactin staining. None of the patients with positive GH staining had acromegalic stigmata and none of the patients with positive prolactin staining had prolactin levels > 100 ng/ml.

47 patients were eligible for the evaluation of recurrent disease. In the microadenoma group, 8 patients out of 32 and in the macroadenoma group, 5 patients out of 15 showed disease recurrence after more than 6 months follow-up. Statistically, there was no difference between relapse of CD in the 2 groups ($p = 0.744$)

The stepwise multiple logistic regression model including age, gender, surgeon's report about the tumour resection, cavernous sinus invasion, suprasellar extension, maximum diameter of adenoma, basal serum cortisol, ACTH, and cortisol-to-ACTH ratio revealed that cavernous sinus invasion was the only negative predictor of remission. A logistic regression model including the same parameters was also performed to detect the indicators of recurrent disease but no predictor could be identified.

Discussion

In this series, we defined clinical and biochemical characteristics of corticotroph macroadenomas and microadenomas. We found that clinical features were significantly different while

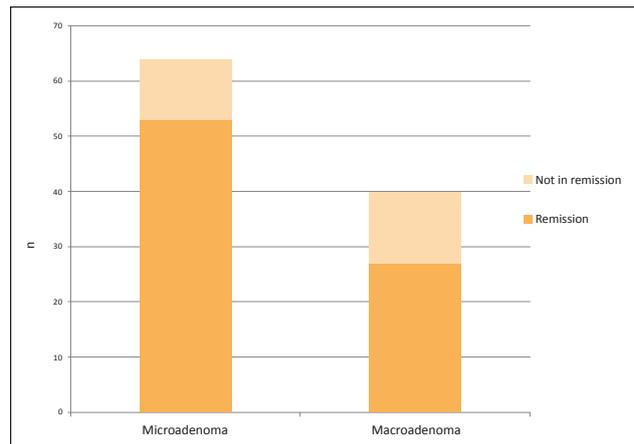


Figure 2. Number of patients in remission after initial surgery.

biochemical evidence of hypercortisolism was similar between macroadenomas and microadenomas.

The frequency of macroadenomas was found to be 37.4 %, which is higher than the prevalence rates in previous reports. Initially, the prevalence of macroadenomas was reported to be approximately 10 %, however, it was stated that due to the selection bias this might be an underestimation [2]. Following articles reported the frequency to range from 6.6–50 % [3, 5, 7, 8]. Being a referral centre, more complicated cases might have been clustered at our centre, including macroadenomas.

There was a female predominance in the microadenoma group whereas gender distribution was equal in the macroadenoma group. Patients with a microadenoma were found to be younger than those with a macroadenoma. Gender distribution (female : male) ranged from 3:1 to 10:1 in Cushing's syndrome, with a mean age of 36 years at diagnosis [9, 10]. In contrast to our series, most of the previous reports about ACTH-positive macroadenomas stated similar age and gender distributions compared to ACTH-positive microadenomas. Similar to our series, Selvais et al reported that patients with a macroadenoma were 10 years older than those with a microadenoma, but this did not reach significance [5].

Main phenotypic features of Cushing's syndrome differed widely between macroadenoma and microadenoma patients in our series. Symptoms of mass effect were clearly significant in macroadenomas while clinical evidences of hypercortisolism including lower lymphocyte counts were fostered more in the group with microadenomas. It is known that degree and duration of hypercortisolism cause differences in the severity of clinical manifestations [11]. Additionally, ACTH-positive macroadenomas were demonstrated to have increased proliferative potentials [2]. Therefore, we think that the faster growth of pituitary mass in macroadenoma patients might be responsible for the lack of classical manifestations of CD.

Furthermore, both ACTH-positive macroadenomas and microadenomas are of monoclonal origin but ACTH-positive macroadenoma patients were reported to have defects in the processing of proopiomelanocortin to ACTH [12, 13]. Our

speculations about ACTH-positive macroadenomas have been mentioned by Katznelson et al who found that clinical manifestations and hypercortisolemia were preceded by the detection of large-sized tumours in theory [2]. These interpretations were also supported by various previous reports [14, 15]. Other than the short manifestation period, glucocorticoid resistance was accused for paucity of signs and symptoms of Cushing's syndrome [7]. Moreover, subtle clinical presentation of Cushing's syndrome is increasingly found in clinical practice [16].

Baseline hormonal characteristics including basal cortisol, ACTH, UFC, and cortisol-to-ACTH ratio of patients with macroadenomas and microadenomas were similar in our series. Postoperative nadir ACTH levels were higher in macroadenoma patients than in microadenoma patients. Whether biochemical parameters of hypercortisolism differ between microadenoma and macroadenoma patients is still being controversially debated in the literature. Earlier reports stated higher levels of ACTH in macroadenomas which were not accompanied by increased serum or urinary cortisol levels [2, 5]. Quite on the contrary, elevated levels of basal cortisol and ACTH were reported in microadenomas by Woo et al [7]. Recently, an article from Korea reported similar levels of basal cortisol, ACTH, UFC, and cortisol-to-ACTH ratio between microadenoma and macroadenoma patients, consistent with the baseline hormonal evaluation of our series [3]. In our series, patients with macroadenomas were less responsive to HDDST than patients with microadenomas, but this did not reach statistical significance. The literature supports impaired glucocorticoid suppressibility after HDDST in macroadenomas and no possible reason for this occurrence could be offered until today [2, 3, 5].

Remission was achieved in 82.8 % of microadenoma and 67.5 % of macroadenoma patients with CD. This is consistent with the previous success rates of initial pituitary surgery. Mampalam et al reported initial remission rates of 53 % in macroadenoma patients and 88 % in microadenoma patients [17]. In the literature, remission rates of macroadenomas range between 53 % and 68 % [14, 17–19]. However, more successful surgeries for microadenomas and macroadenomas have also been reported [4, 8]. We found cavernous-sinus invasion to be the only negative predictor of remission. Accordingly, invasiveness of the tumour was correlated with an unfavorable outcome in earlier studies [14, 18]. MRI failed to demonstrate a tumour in 7 patients. Four of the 6 patients (66.7 %) with an invisible tumour at MRI scan were in remission after initial surgery.

One third of the patients in each group, who were followed up for > 6 months, were found to have relapsed. Blevins et al observed recurrence in 36 % of macroadenomas, which is similar to our findings, and in 12 % of microadenomas (lower than our recurrence rate) [18]. Fomekong et al reported recurrence in 14 % of microadenoma patients and none of the macroadenoma patients [8]. Patil et al reported the recurrence rate in patients followed beyond 6 months to be 17.4 % and also stated that when follow-up lasted for > 5 years, the recurrence rate would increase up to 46 % [20]. We defined recurrence in patients followed > 6 months and recurrence rates in both mi-

croadenomas and macroadenomas seems to be higher. However, we were not able to detect any predictor of recurrence in our series.

In conclusion, patients with corticotroph macroadenomas and microadenomas share similar biochemical evidence of hypercortisolism as well as remission and recurrence rates but the presentation of clinical manifestations is significantly different. Cavernous-sinus invasion was found to be a negative predictor of remission.

■ Practical Relevance

Prevalence of pituitary corticotroph macroadenomas was higher than presumed. Although patients with corticotroph macroadenomas and microadenomas share similar biochemical evidence of hypercortisolism, remission and recurrence rates, their clinical manifestations are significantly different. The more subtle clinical presentation of patients with corticotroph macroadenomas may have been due to a shorter manifestation time because of more progressive tumour growth.

■ Declaration of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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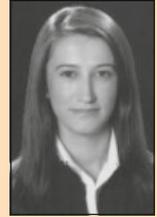
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