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Research Article

Clinical and Demographic Characteristics of Patients with Non-Functional Pituitary Adenomas: A Retrospective Single-Center Study

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Abstract

Objectives: Non-functioning pituitary adenomas (NFPAs) are typically diagnosed due to tumor mass effects rather than hormone hypersecretion. However, variability in clinical presentation and outcomes remains incompletely defined.

Methods: This retrospective study included 200 patients diagnosed with NFPAs between 2013 and 2020. Clinical features, hormonal parameters, tumor size, and follow-up outcomes were analyzed.

Results: The mean age at diagnosis was 41.31 years. Macroadenomas were more frequent in males, whereas microadenomas predominated in females (p=0.002). Headache, hypogonadal symptoms, and fatigue were the most common presenting complaints. Mass effect–related symptoms were more prominent in males and larger tumors (p<0.05). The most frequent hormonal abnormalities were growth hormone deficiency (22%), central hypogonadism (17.5%), and central hypothyroidism (15.5%), with a higher prevalence in larger tumors (p<0.05). Visual field defects were identified in 16% of patients and were strongly associated with larger tumors (p<0.001). Tumor size remained stable at one year, although new hormonal deficiencies developed during follow-up.

Conclusion: NFPAs demonstrate distinct sex- and size-related clinical patterns. Men tend to present later with larger tumors and a higher burden of mass effect–related symptoms. Progressive endocrine dysfunction may occur despite radiological stability, underscoring the need for long-term follow-up.

Keywords: Hypopituitarism, macroadenoma, non-functioning pituitary adenoma, pituitary incidentaloma, transsphenoidal surgery

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Pituitary adenomas are among the most common intracranial tumors, accounting for approximately 10–15% of all primary brain neoplasms. These tumors arise from adenohypophyseal cells and are broadly classified as functional or non-functional based on their hormonal activity. Pituitary adenomas are also classified by tumor size: lesions <10 mm are defined as microadenomas, ≥10 mm as macroadenomas, and ≥40 mm as giant adenomas.[1,2]

Most pituitary adenomas present with clinical findings related to hormone hypersecretion, such as hyperprolactinemia, acromegaly, and Cushing's disease. However, approximately 25–35% of pituitary adenomas are clinically silent and are classified as non-functioning pituitary adenomas (NFPAs).[3] NFPAs represent one of the most common subtypes of pituitary adenomas and are defined by the absence of clinically significant hormone hypersecretion.

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NFPAs are frequently detected incidentally on imaging performed for unrelated indications (pituitary incidentalomas) or become clinically evident due to local mass effects, most commonly hypopituitarism, headache, and visual field defects resulting from optic chiasm compression.[4-6] Consequently, the absence of clinically significant hormone hypersecretion often delays diagnosis until tumor enlargement produces compressive symptoms.

Although classified as non-functioning, NFPAs constitute a biologically heterogeneous group. Some tumors demonstrate no evidence of hormone production, whereas others show positive immunohistochemical staining for pituitary hormones without clinically evident hormone excess. These lesions are therefore referred to as clinically silent adenomas.[7,8]

Approximately 70–90% of clinically non-functioning pituitary adenomas are gonadotroph adenomas, arising from cells capable of producing follicle-stimulating hormone (FSH) and luteinizing hormone (LH).[9] Owing to their limited hormonal activity, patients typically present with symptoms related to local tumor expansion, including visual disturbances, headache, and varying degrees of pituitary dysfunction.[10] In addition, clinically silent variants of somatotroph, corticotroph, thyrotroph, and lactotroph adenomas have also been described, demonstrating immunohistochemical hormone expression without corresponding clinical syndromes.[11-15]

After the detection of a pituitary adenoma, evaluation should focus on the presence of hormone hypersecretion and symptoms related to tumor mass effects. In patients with NFPA, the primary goals of treatment are relief of compressive symptoms, preservation or improvement of pituitary function, and prevention of tumor progression or recurrence. Transsphenoidal surgical resection is considered the standard first-line treatment modality, and surgery is generally recommended in the presence of compressive symptoms or documented tumor growth. Radiotherapy is infrequently used as primary treatment and is mainly reserved for patients unsuitable for surgery or as adjuvant therapy for residual disease. No medical therapy has demonstrated clear efficacy in NFPAs. Patients managed with observation are typically monitored every 3–6 months with clinical and radiological follow-up.[16]

The aim of this retrospective study was to evaluate the clinical, radiological, and pathological characteristics of patients diagnosed with non-functioning pituitary adenoma and to identify factors associated with tumor progression, recurrence, and treatment outcomes. In addition, we sought to assess the impact of tumor size, invasiveness, and treatment modalities on disease course and follow-up outcomes.

Methods

This retrospective cross-sectional study was conducted following approval from a Mersin University Ethics Committee (Decision no: 347, dated May 13, 2020). Patient records of individuals diagnosed with NFPA and managed between January 1, 2013, and March 31, 2020, at a tertiary referral center were systematically reviewed. The study was carried out in accordance with the principles of the Declaration of Helsinki.

Inclusion criteria were age between 18 and 65 years and confirmed diagnosis based on clinical, hormonal, and radiological findings. Patients with incomplete hormonal evaluation or insufficient imaging data were excluded. A total of 200 patients (137 female, 63 male) were included. Demographic data, presenting symptoms, baseline hormonal parameters (PRL, FSH, LH, ACTH, TSH, cortisol, GH, IGF-1), tumor size, and imaging findings were recorded. Adenomas were classified as microadenomas (<10 mm) or macroadenomas (≥10 mm).

Patients were categorized according to treatment approach (surgical vs. non-surgical) and follow-up status. Follow-up duration, hormonal deficiencies, visual field defects, residual tumor, recurrence, and additional treatment requirements were evaluated.

Statistical Analysis

Statistical analyses were performed using STATISTICA version 13.5 (TIBCO Software Inc., Palo Alto, CA, USA). The normality of data distribution was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Continuous variables were expressed as mean ± standard deviation or as minimum–maximum values, depending on the distribution characteristics, while categorical variables were presented as frequencies (n) and percentages (%). Comparisons of continuous variables, including age at diagnosis, hormone levels, and tumor size, according to sex and tumor classification (microadenoma vs. macroadenoma), were performed using the independent samples t-test. Comparisons of categorical variables, such as presenting symptoms and hormonal abnormalities, were conducted using the chi-square test or Fisher's exact test when appropriate. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

Results

A total of 200 patients were included in the study, of whom 137 (68.5%) were female and 63 (31.5%) were male. Microadenomas were detected in 106 patients, and macroadenomas were detected in 94 patients. Microadenomas were more commonly observed in females (60.6% vs.

36.5%), whereas macroadenomas were significantly more frequent in males (63.5% vs. 39.4%), and both of these differences were statistically significant (p=0.002). The mean age at diagnosis was 41.31±15.36 years. Male patients were diagnosed at a significantly older age than female patients (47.54±18.33 vs. 38.44±12.87 years). Similarly, patients with macroadenomas were older than those with microadenomas (49.09±15.98 vs. 34.41±10.88 years, p<0.001).

The most common presenting symptoms were headache, hypogonadal symptoms (menstrual irregularity, decreased libido, and impotence), and fatigue. In female patients, the most frequent symptoms were headache (59.9%), menstrual irregularity (44.5%), and fatigue (19%), whereas in male patients, headache (79.4%), fatigue (34.9%), and decreased libido (34.9%) were more prominent. Headache, visual disturbance, ophthalmoplegia, and fatigue were significantly more frequent in male patients (p<0.05). Table 1 shows the distribution of presenting symptoms according to sex.

When stratified by tumor size, patients with macroadenomas more commonly presented with headache, visual disturbance, and ophthalmoplegia, whereas hypogonadal symptoms and galactorrhea were more frequently observed in patients with microadenomas (p<0.001). Importantly, in all patients presenting with galactorrhea, the symptom was attributed to non-pituitary causes, and NFPA was identified incidentally during the diagnostic workup. Visual field defects were detected in 32 patients (16%), with a significantly higher prevalence in macroadenomas compared to microadenomas (32% vs. 0.9%, p<0.001) (Table 2).

The most common hormonal abnormalities were growth hormone deficiency (22%), central hypogonadism (17.5%), and central hypothyroidism (15.5%). In male patients, growth hormone deficiency (34.9%), central hypogonadism (25.4%), and central hypothyroidism were the most frequent abnormalities, whereas in female patients, hyperprolactinemia (18.2%), growth hormone deficiency (16%), and central hypogonadism (13.9%) were more common. Growth hormone deficiency (p=0.005) and central hypothyroidism (p = 0.035) were significantly more frequent in male patients, while hyperprolactinemia was more common in female patients (p=0.016). Hormonal abnormalities were more prevalent in macroadenomas, particularly central hypogonadism (24%), central hypothyroidism (23.4%), and growth hormone deficiency (28.7%) (p<0.05). The distribution of hormonal abnormalities according to tumor size and sex is presented in Tables 3 and 4, respectively.

Regarding the initial point of contact, the majority of patients presented to the neurosurgery (n=79, 39.5%) and endocrinology (n=71, 35.5%) departments, while the remainder visited neurology (n=20, 10%), obstetrics and gynecology (n=11, 5.5%), and other clinics (n=19, 9.5%),

Table 1. Distribution of presenting symptoms according to sex

Symptom	Female (n=137), n (%)	Male (n=63), n (%)	p
Headache	82 (59.9)	50 (79.4)	0.007
Blurred vision	26 (19.0)	21 (33.3)	0.032
Ophthalmoplegia	4 (2.9)	7 (11.1)	0.038
Fatigue	26 (19.0)	22 (34.9)	0.020
Decreased libido	26 (19.0)	22 (34.9)	—
Menstrual irregularity	61 (44.5)	—	—
Galactorrhea	25 (18.2)	1 (1.6)	0.016
Short stature	0 (0.0)	1 (1.6)	—
Impotence	—	17 (27.0)	—
Weight change	5 (3.6)	2 (3.2)	—

Table 2. Distribution of presenting symptoms according to tumor size

Symptoms	Microadenoma (n=106), n (%)	Macroadenoma (n=94), n (%)	p
Headache	48 (45.3)	84 (89.4)	<0.001
Blurred vision	12 (11.3)	35 (37.2)	<0.001
Ophthalmoplegia	0 (0.0)	11 (11.7)	<0.001
Fatigue	22 (20.8)	26 (27.7)	—
Hypogonadal symptoms (menstrual irregularity, decreased libido, impotence)	60 (56.6)	25 (26.6)	<0.001
Short stature	1 (0.9)	0 (0.0)	—
Weight change	4 (3.8)	3 (3.2)	—
Galactorrhea	24 (22.6)	2 (2.1)	<0.001

Table 3. Distribution of hormonal abnormalities according to tumor size

Hormonal abnormality	Macroadenoma (n=94), n (%)	Microadenoma (n=106), n (%)	p
Hyperprolactinemia	16 (17.0)	14 (13.2)	—
Hypoprolactinemia	8 (8.5)	3 (2.8)	—
Central hypogonadism	22 (23.4)	13 (12.3)	0.042
Central hypothyroidism	22 (23.4)	9 (8.5)	0.006
Cortisol deficiency	18 (19.1)	7 (6.6)	0.017
Growth hormone deficiency	27 (28.7)	17 (16.0)	0.040

Table 4. Distribution of hormonal abnormalities according to sex

Hormonal abnormality	Male (n=63), n (%)	Female (n=137), n (%)	p
Hyperprolactinemia	5 (7.9)	25 (18.2)	0.016
Hypoprolactinemia	7 (11.1)	4 (2.9)	—
Central hypogonadism	16 (25.4)	19 (13.9)	—
Central hypothyroidism	15 (23.8)	16 (11.7)	0.035
Cortisol deficiency	13 (20.6)	12 (8.8)	—
Growth hormone deficiency	22 (34.9)	22 (16.1)	0.005

including the emergency department, ophthalmology, general surgery, and urology.

Visual field examination was performed in all patients at initial presentation, revealing adenoma-related visual field defects in 32 patients (16%), including 1 patient (0.9%) with microadenoma and 31 patients (32%) with macroadenoma, with a significantly higher prevalence observed in macroadenomas ($p<0.001$). Notably, the microadenoma associated with visual field defect measured 9.5 mm and was located in close proximity to the optic chiasm.

Among the 112 patients who remained in follow-up, surgical intervention was performed in 41 cases, predominantly in those with macroadenomas ($p < 0.001$). Surgical indications mainly included optic chiasm compression, hormonal deficiencies, and persistent headache. Residual tumor was detected in 20 patients (48%), and recurrence occurred in 7 patients (17.1%). Postoperative hormonal evaluation showed that 12 patients (29.3%) had normal hormone profiles, 20 patients (48.8%) had panhypopituitarism, and the remaining 9 patients had one or more hormonal deficiencies. Postoperative radiotherapy was required in 8 patients (19.5%). Patients managed conservatively were followed at 3–6 month intervals, and a minority developed new hormonal deficiencies, including hypoprolactinemia, central hypogonadism, and growth hormone deficiency during follow-up.

Follow-up MRI at one year demonstrated no meaningful change in tumor size among 54 non-operated patients, with comparable mean diameters at baseline and at one year (8.74±6.34 mm vs. 8.69±6.09 mm).

Discussion

Non-functioning pituitary adenomas (NFPAs) demonstrate variability in demographic characteristics across different study populations. Previous studies have reported that NFPAs are more common in females before the fourth decade of life, whereas male predominance becomes more apparent in the later decades.[17-20] In addition, several reports have indicated that diagnosis typically occurs in the fifth decade in females and in the sixth decade in males, with an overall mean age ranging between 50 and 55 years.[18]

In line with previous studies, female patients constituted the majority in our cohort, and men were diagnosed at a significantly older age than women (47.54±18.33 vs. 38.44±12.87 years). Overall, the mean age at diagnosis in our cohort was lower than that reported in the literature. This difference may be attributed to earlier imaging, greater accessibility to healthcare, or differences in referral patterns. The statistically significant age difference between sexes and between tumor size groups suggests that tumor growth and delayed clinical presentation are closely related.

Consistent with previous studies, macroadenomas were more frequently observed in males, whereas microadenomas predominated in females. In addition, patients with macroadenomas were diagnosed at older ages compared to those with microadenomas, which is likely related to the absence of early endocrine symptoms and the delayed development of mass effect–related clinical findings. These findings are in line with prior reports demonstrating that tumor size is associated with both age at diagnosis and clinical presentation.

The initial point of healthcare contact for patients with NFPA remains an underexplored area in the literature. While some studies have suggested that patients commonly present to ophthalmology clinics,[21] our findings indicate that the majority of patients initially presented to neurosurgery outpatient clinics, likely due to the high prevalence of headache as the presenting symptom. Only a minority of patients presented initially to endocrinology clinics, highlighting the importance of multidisciplinary evaluation in these patients.

In our cohort, the most common presenting symptoms were headache, hypogonadal symptoms, and fatigue, which are consistent with the known effects of tumor mass and pituitary dysfunction. Although symptom distribution varies across populations, our findings were largely in agreement with previous studies.[16,18,19,22-26] Evidence regarding sex-related differences in the presenting symptoms of non-functioning pituitary adenomas remains limited and, at times, inconsistent across studies. Di Somma et al.[25] reported a higher prevalence of headache and visual disturbances in male patients, whereas other analyses did not demonstrate a clear association between headache and sex.[27] Similarly, Ferrante et al.[19] observed comparable rates of hypogonadal symptoms between females and males (42.5% vs. 37.9%)[19], while Cury et al.[28] reported a markedly higher prevalence in females (78% vs. 35%)[28]. In contrast to these heterogeneous findings, our results sug-

gest a more distinct sex-related pattern of clinical presentation. Specifically, male patients in our cohort more frequently exhibited symptoms related to tumor mass effect, including headache, visual disturbance, ophthalmoplegia, and fatigue. Our findings indicate a distinct sex-related pattern in clinical presentation, likely reflecting differences in tumor burden as well as variations in symptom perception and referral pathways.

Tumor size also played a significant role in symptom presentation. Patients with macroadenomas more frequently presented with symptoms related to local mass effect, including headache, visual disturbance, and ophthalmoplegia, whereas hypogonadal symptoms and galactorrhea were more commonly observed in microadenomas. These findings are consistent with prior reports showing that mass effect–related symptoms are more prominent in larger tumors.[29]

Previous studies have reported a wide range in the prevalence of hormonal abnormalities in non-functioning pituitary adenomas, varying between 30% and 85%, while panhypopituitarism has been reported in approximately 10% of cases. The most frequently described deficiencies include growth hormone deficiency (61–100%), gonadotropin deficiency (36–96%), and adrenal insufficiency (17–62%), although these rates differ substantially depending on the studied population and diagnostic criteria.[16,19,30,31] In comparison, our cohort demonstrated a lower overall frequency of hormonal abnormalities, with growth hormone deficiency (22%), central hypogonadism (17.5%), and central hypothyroidism (15.5%) being the most common findings. This discrepancy may be attributed to differences in patient selection, earlier-stage disease at diagnosis, or the retrospective nature of our study. Notably, new hormonal abnormalities developed during follow-up in a subset of patients, suggesting a dynamic and potentially progressive course of pituitary dysfunction.

Sex-based differences in hormonal abnormalities were also evident. Growth hormone deficiency and central hypothyroidism were significantly more frequent in males, whereas hyperprolactinemia was more commonly observed in females. Although partially consistent with previous studies, these findings also highlight variability across different cohorts, which may reflect differences in tumor characteristics, hormonal evaluation methods, and population-specific factors.

Hormonal dysfunction was more pronounced in patients with macroadenomas. Central hypogonadism, central hypothyroidism, cortisol deficiency, and growth hormone deficiency were all significantly more frequent in macroadenomas, supporting the concept that larger tumors exert a greater mass effect on normal pituitary tissue. These findings are consistent with previous studies demonstrating a strong association between tumor size and hypopituitarism.

Visual impairment is a well-recognized complication of NFPAs, primarily resulting from compression of the optic chiasm. Previous studies have reported visual field defects in approximately one-third of patients. In our cohort, visual field defects were identified in 16% of patients at initial endocrinology outpatient evaluation and were significantly more frequent in macroadenomas. Notably, the only microadenoma associated with a visual field defect measured 9.5 mm and was located in close proximity to the optic chiasm, emphasizing the importance of tumor location in addition to size.

Surgical management remains the mainstay of treatment in symptomatic patients. In our study, all operated patients underwent transsphenoidal surgery. Postoperatively, a substantial proportion of patients had persistent hormonal deficiencies, and nearly half had residual tumor tissue. Recurrence and the need for adjuvant radiotherapy were observed in 17.1% (n=7) and 19.5% (n=8) of patients, respectively. These findings are consistent with previous reports indicating that complete resection is often challenging due to tumor size and invasiveness.[5,19,32-34]

Long-term follow-up is essential in patients with NFPAs. In our study, newly developed hormonal abnormalities were observed during follow-up, despite overall stability in tumor size. Among non-operated patients with available imaging at one year, no significant change in tumor size was detected, in line with previous studies suggesting that a considerable proportion of NFPAs remain stable over time. However, the emergence of new hormonal abnormalities underscores the need for regular endocrine evaluation, even in patients managed conservatively.

Several limitations of this study should be acknowledged. The retrospective design and single-center setting may have influenced the interpretation of the findings; however, the comprehensive clinical characterization and real-world data provide meaningful insight into the clinical behavior of NFPAs.

Conclusion

In conclusion, this study provides a comprehensive characterization of patients with non-functioning pituitary adenomas, demonstrating that delayed diagnosis—particularly in male patients—is associated with a higher prevalence of macroadenomas and a predominance of mass effect–driven presentation. Additionally, the observed sex-specific differences in clinical features suggest that both biological

and diagnostic factors may influence disease recognition and should be considered in clinical evaluation.

Importantly, our findings highlight the dynamic nature of pituitary dysfunction in NFPAs, as hormonal axes that are initially preserved may deteriorate over time, even in the absence of overt radiological tumor progression. Furthermore, the high frequency of residual disease and recurrence following surgical intervention underscores the need for long-term, multidisciplinary follow-up. Taken together, these findings support a more individualized and longitudinal approach to NFPA management. Future prospective, multicenter studies incorporating standardized follow-up strategies are warranted to further refine surveillance and improve patient outcomes.

Disclosures

Ethics Committee Approval: This retrospective cross-sectional study was conducted following approval from a Mersin University Ethics Committee (decision no: 347, dated May 13, 2020).

Informed Consent: Informed consent was not obtained due to the retrospective design of the study.

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