



Original Article (BRAIN)

Frequency of Functional and Non-Functional Pituitary Adenomas in Patients Presented at Ayub Teaching Hospital, Abbottabad

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ABSTRACT

Objective: Pituitary lesions cause morbidity and mortality in all age groups due to their hormonal hypersecretion, its mass effects, and post-surgery complications. The present study determined the frequency of functional and non-functional pituitary adenomas.

Materials & Methods: The study included patients (n = 114) presenting with functional and non-functional pituitary adenoma. Pituitary adenomas were diagnosed based on MRI brain with contrast and the size of the tumor was noted a tumor having a size of 10 mm or more was labeled as macro adenoma and a tumor having a size less than 10 mm was labeled as microadenoma. Pituitary adenomas were stratified among age, gender, duration of symptoms, types of adenomas, types of functional adenoma, and type of the tumor on a size basis.

Results: Most of the patients had TSH- secreting adenoma (21.9%). 52.6% were found with microadenoma and 47.4% had macro adenoma. Patients with functional adenoma were 30.7% and with non-functional adenoma 32.5% were male while patients with functional adenoma were 26.3% and with non-functional adenoma 10.5% were female (p = 0.018). Patients with functional adenoma (43.9%) and non-functional adenoma (8.8%) were found to have microadenoma, whereas patients with functional adenoma (13.2%) and non-functional adenoma (34.2%) were found to have macroadenoma (p = 0.000). Patients with functional adenoma having a duration of symptoms below 1 year were 11 (9.6%), 1 to 3 years were 25 (21.9%), 17 (14.9%) were 4 to 6 years, and 12 (10.5%) above 6 years duration of symptoms.

Conclusion: Patients with pituitary adenomas should be diagnosed early to receive successful therapy.

Keywords: Functional/Non-functional Adenoma, Pituitary Adenomas.

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INTRODUCTION

The pituitary gland is situated in the pituitary fossa in the middle cranial fossa and is functionally linked to the hypothalamus. It is also called the master gland and play important role in controlling and regulating other hormone-producing glands.¹ Pituitary lesions are classified based on underlying etiology. Pituitary masses may be adenomas, hyperplasia, non-adenoma tumors, vascular or inflammatory, or infective lesions.² Pituitary lesions cause morbidity and mortality in all age groups worldwide due to their hormonal hypersecretion, its mass effects, and post-surgery complications.

Pituitary adenomas are the third most common intracranial tumors making up 8 % of all brain tumors in adults.³ The adenomas have the same prevalence in both genders but the prolactinomas are more common in females.^{4,5} About 20% of the pituitary masses are found incidentally on the autopsies reports.⁶ Pituitary adenomas secrete hormones depending upon the primary cell origin and its effects on another gland. Few adenomas hyper secrete the hormones and they are clinically manifested and are thus termed as Functional adenomas while few adenomas do not secrete sufficient hormones which are detectable on the blood test or which can be clinically manifested.⁷⁻⁸ Prolactinoma is the most prevalent functional adenoma estimating about 40 – 57% of all pituitary adenoma. Nonfunctioning adenomas are the second most prevalent pituitary adenoma making up 14 – 54% of all pituitary tumors.⁹

Pituitary adenomas are also classified based on their size. Tumors having a size of 10mm or more are called macro adenomas and those having a size of less than 10mm are called microadenomas. Macro adenomas are slightly more common making 57.4% of the pituitary adenomas.¹⁰ The clinical manifestations of the adenomas depend upon the type of the adenomas. Headache fatigue erectile dysfunction,

gynecomastia weakness decreased visual acuity, vomiting, anorexia, bitemporal hemianopia, etc., are some of the clinical manifestations depending on the type and secretion of the hormone.¹¹ The adenomas are diagnosed by hormonal studies and radiological studies. The treatment of pituitary adenomas is multidisciplinary involving an endocrinologist, neurosurgeon, radiologist, and oncologist. Treatment of pituitary adenomas depends upon the type of the tumor. The treatment choices for adenomas are observation, medical therapy, surgical therapy, hormonal treatment, and radiotherapy.¹²⁻¹³ Going through the literature search it was observed that 10 % of the pituitary adenomas are existing in the normal population on MRI findings diagnosed incidentally. Our study will help us to know the frequency of adenomas and types of adenomas. This will help us in screening patients for adenomas if it is suspected depending on the signs and symptoms. This study will surely add up to the existing literature and will help us in the reduction of morbidity and mortality through early diagnosis and proper management.

Reliable epidemiological statistics on pituitary adenomas (PAs) are critical for evaluating the impact on the healthcare system and establishing effective resource allocation for clinical care and research. According to cross-sectional research from Switzerland, Belgium, and the United Kingdom, the prevalence of PAs ranges from 78 to 94 instances per 100,000 people (three to five times higher than previously thought). The statistics from Northern Finland revealed an overall standardized incidence rate of 4 per 100,000, with accidentally detected cases increasing. The increased knowledge of pituitary dysfunction, as well as recent developments in testing tools, have aided in the early identification of PAs. To have a better understanding of the epidemiology of PAs, further studies with a broad population and a bigger sample size are required.¹⁴

MATERIAL AND METHODS

Study Design & Setting

A cross-sectional design study was conducted in the Neurosurgery Department of the Ayub Teaching Hospital, Abbottabad, the hospital covers patients from a large northern area of Pakistan. The duration of the study was about 6 months i.e., from July 2020 to December 2020.

Inclusion Criteria

All the patients of both genders, who were in the age range – of 18 to 60 years (avoiding a wide range) were included.

Exclusion Criteria

Treated cases were excluded. Patients who were using drugs that cause hormonal imbalances were not included. Also, pregnant women were not included.

Sampling

The sample size was 114 as calculated keeping an 8% prevalence³ of pituitary adenomas in intracranial tumors, the confidence level of 95 percent, and the margin of error was about 5 percent calculated based on the EPI sample size calculator. This was a consecutive nonprobability sampling.

Data Collection Procedure

The study has been conducted after getting approval from the ethical committee of Ayub Teaching Hospital. Those Patients that presented in OPD fulfilling the criteria for inclusion were admitted to the Neurosurgery ward and get enrolled in the study after taking informed written consent from the patient or guardian. Routine investigations, detailed history, and clinical examination were performed.

Clinical Management

Pituitary adenomas were diagnosed based on MRI brain with contrast and the size of the tumor was noted a tumor having a size of 10mm or more was labeled as macro adenoma and a tumor having a size less than 10mm was labeled as microadenoma. After inclusion, 10 CC of blood was obtained in all the patients and was immediately sent to the hospital laboratory for detecting the pituitary hormonal study by standard radio-immunoassay methods including ACTH, IGF- 1, FSH/LH, estradiol, or testosterone level, prolactin (PRL), TSH, and GH. All the laboratory investigations were done from a single hospital laboratory under the supervision of an expert pathologist. All the above-mentioned information and as age, BMI, gender, duration of symptoms, types of adenoma (functional and non-functional), types of functional adenoma, and type of the tumor on a size basis (microadenoma or macro adenoma) were recorded in a predesigned proforma. Strictly the patients with criteria of exclusion were marked to minimize the confounding error and bias in the study results.

Data Analysis

The analysis of data was done on SPSS 26. Mean and standard deviation was used to calculate the quantitative variable like BMI, age, and duration of symptoms. While the qualitative variables like gender, types of adenomas (functional and non-functional), type of functional adenoma, and type of the tumor on size basis (microadenoma or macro adenoma) were calculated in percentages and frequencies. Pituitary adenomas were stratified among age, gender, duration of symptoms, types of adenomas (functional and non-functional), types of functional adenoma, and type of the tumor on a size basis (microadenoma or macro adenoma) to see effect modifications. The p-value of less than 0.05 was considered significant which was calculated through the chi-square test after the stratification of data.

RESULTS

The present study with a sample of 114 patients was conducted to find out the frequency of functional and nonfunctional pituitary adenoma in patients presented at the Department of Neurosurgery, Ayub Teaching Hospital Abbottabad.

Age Information

The mean age of the patients was 41.22 ± 12.584 ranging from 18 to 60 years.

Information of BMI

The mean BMI was 22.44 ± 4.315 ranging from 17 to 33 kg/m², out of a total of 114 patients (Table 1).

Gender Distribution

Most of the patients in our study were 72 (63.2%) male and 42 (36.8%) female out of 114 patients.

Frequency of Symptoms

In the frequency or duration of symptoms, most of the patients had 1 to 3 years duration of symptoms i.e., 61 (53.5%), 4 to 6 years duration was 21 (18.4%), below 1 year was 17 (14.9%) and 15 (13.2%) had more than 6-year duration, out of total 114 patients (Table 2).

Table 2: Presenting Symptoms (n = 114).

Duration of Symptoms	Prevalence	Percentage
1 – 3 years	61	53.5%
4 – 6 years	21	18.4%
Less than 1 year	17	14.9%
More than 6 years	15	13.2%

Types of Adenoma

Most of the patients in our study had 65 (57.0%)

Table 1: Information on Age and BMI (n = 114).

Parameters	Minimum	Maximum	Mean	Std. Deviation
Age	18	60	41.22	12.584
BMI	17	33	22.44	4.315

functional and 49 (43.0%) non-functional adenomas out of 114 patients (Table 3).

Table 3: Frequency of Types of Adenoma.

Adenoma	Frequency	Percent
Functional	65	57.0
Nonfunctional	49	43.0
Total	114	100.0

Types of Functional Adenoma

In the frequency of types of functional adenoma, most of the patients had TSH- secreting adenoma i.e., 25 (21.9%), 17 (14.9%) had ACTH-secreting adenomas, 12 (10.5%) had prolactinoma and 11 (9.6%) had growth hormone (GH) secreting adenoma, out of total 114 patients (Table 4). 43% were having nonfunctional adenomas.

Table 4: Frequency of Types of Functional Adenoma.

Functional Adenoma	Frequency	Percent
Prolactinoma	12	10.5
TSH-secreting adenoma	25	21.9
Growth hormone (GH)- secreting adenoma	11	9.6
ACTH-secreting adenomas	17	14.9
Nonfunctional	49	43.0
Total	114	100.0

Micro/Macro Adenoma

Most of the patients in our study in the frequency of the type of the tumor on the size on MRI findings, 60 (52.6%) found micro adenoma and 54 (47.4%) had macro adenoma, out of 114 patients (Table 5).

Age Distribution w.r.t Adenoma Type

In frequency distribution of age concerning types of adenoma, patients with functional adenoma were 30 (26.3%) and those with non-functional adenoma were 30 (26.3%) in the age group of 18 to 40 years while patients with functional adenoma were 35 (30.7%) and with non-functional adenoma was 19 (16.7%) in the age group of 41 to 60 years. This finding was statistically not significant at $p = 0.111$, out of a total of 114 patients (Table 6).

Gender Distribution w.r.t Adenoma Type

In frequency distribution of gender concerning types of adenoma, patients with functional adenoma were 35 (30.7%) and with non-functional adenoma 37 (32.5%) were male while patients with functional adenoma were 30 (26.3%) and with non-functional adenoma 12 (10.5%) were female. This finding was statistically significant at $p = 0.018$, out of a total of 114 patients (Table 7).

Micro/Macro Adenoma w.r.t Adenoma Type

In frequency distribution of type of the tumor on size basis on MRI findings with respect to types of adenoma, patients with functional adenoma were 50 (43.9%) and with non-functional adenoma 10 (8.8%) were found with microadenoma while patients with functional adenoma were 15 (13.2%) and with non-functional adenoma 39 (34.2%) were found with macro adenoma. This finding is statistically significant at $p = 0.000$, out of a total of 114 patients (Table 8).

Table 5: Frequency of type of the tumor on size basis on MRI findings.

Type of Tumor as per MRI	Frequency	Percent
Micro adenoma (< 10mm)	60	52.6
Macro adenoma (≥ 10mm)	54	47.4
Total	114	100.0

Table 6: Frequency distribution of age with respect to types of adenoma.

Age Group	Types of Adenoma		Total	p-value
	Functional	Non-functional		
18 to 40 years	30 26.3%	30 26.3%	60 52.6%	0.111 (insignificant result)
41 to 60 years	35 30.7%	19 16.7%	54 47.4%	
Total	65 57.0%	49 43.0%	114 100.0%	

Table 7: Frequency of gender with respect to types of adenoma.

		Types of adenoma		Total	p-value
		Functional	Non-functional		
Gender	Male	35 30.7%	37 32.5%	72 63.2%	0.018 (significant result)
	Female	30 26.3%	12 10.5%	42 36.8%	
Total		65 57.0%	49 43.0%	114 100.0%	

In frequency distribution of duration of symptoms with respect to types of adenoma, patients with functional adenoma having a duration of symptoms below 1 year were 11 (9.6%), 1 to 3 years were 25 (21.9%), 4 to 6 years were 17 (14.9%) and 12 (10.5%) above 6 years duration of symptoms while patients with non-functional adenoma having a duration of symptoms below 1 year were 6 (5.3%), 1 to 3 years were 36 (31.6%), 4 to 6 years were 4 (3.5%) and 3 (2.6%) above 6 years duration of symptoms. This finding was statistically significant at $p = 0.002$, out of a total of 114 patients (Table 10).

Table 9: Frequency distribution of type of the tumor on size basis on MRI findings with respect to types of adenoma.

Type of the tumor on size basis on MRI findings	Types of adenoma		Total	p-value
	Functional	Non-functional		
Micro adenoma (< 10mm)	50 43.9%	10 8.8%	60 52.6%	0.000 (significant result)
Macro adenoma ($\geq$ 10mm)	15 13.2%	39 34.2%	54 47.4%	
Total	65 57.0%	49 43.0%	114 100.0%	

Table 10: Frequency distribution of duration of symptoms with respect to types of adenoma.

Duration of symptoms	Types of adenoma		Total	p-value
	Functional	Non-functional		
< one year	11 9.6%	6 5.3%	17 14.9%	0.002 (significant result)
1 to 3 years	25 21.9%	36 31.6%	61 53.5%	
4 to 6 years	17 14.9%	4 3.5%	21 18.4%	
> 6 years	12 10.5%	3 2.6%	15 13.2%	
Total	65 57.0%	49 43.0%	114 100.0%	

DISCUSSION

Pituitary adenomas are classified as macroadenomas (diameters greater than 10 mm) or microadenomas (diameters less than 10 mm), and those with a diameter greater than 40 mm are also known as gigantic adenomas. Furthermore, PAs are characterized as functioning or non-functioning based on whether or not they have a hormonal hypersecretory capability. Functioning PAs are categorized as prolactin-, growth hormone (GH)-, adrenocorticotrophic hormone (ACTH)-, or thyrotropin-producing adenomas based on the type of hormone emitted. A third of PAs are non-functioning, usually, macroadenomas that produce gonadotropin or prolactin but do not cause symptoms due to hormonal hypersecretion.¹⁵ The

present study with a sample of 114 patients was conducted to find out the frequency of functional and nonfunctional pituitary adenoma in patients presented at the Department of Neurosurgery, Ayub Teaching Hospital Abbottabad. The mean age of the patients was 41 years, ranging from 18 to 60 years and the mean BMI was 22.44 ± 4.315 ranging from 17 to 33 kg/m². The mean age of the patients was found almost similar to the patients included in the study conducted by Daly et al.¹⁰

Non-functioning pituitary adenomas account for 14 – 54 percent of pituitary adenomas and have a 7 – 41.3/100,000 population prevalence. Because of their huge size, NFPAs (non-functioning pituitary adenomas) might be entirely asymptomatic or cause substantial hypothalamic/pituitary dysfunction and visual field impairment.

Most patients report symptoms of mass effects, such as headaches, visual field abnormalities, ophthalmoplegias, and hypopituitarism, although pituitary stalk deviation can also cause hyperprolactinaemia and, less commonly, pituitary apoplexy. Non-functioning pituitary incidentalomas are discovered during an unrelated brain imaging procedure.⁹ Most of our patients were 72 (63.2%) male and 42 (36.8%) female while in the frequency of duration of symptoms, most of the patients had 1 to 3 years duration of symptoms i.e., 61 (53.5%), 4 to 6 years duration was 21 (18.4%), below 1 year was 17 (14.9%) and 15 (13.2%) had more than 6-year duration. Most of our patients had 65 (57.0%) functional and 49 (43.0%) non-functional adenoma. In a study conducted by Ntali and Wass⁹, almost similar results were found, while in the frequency of types of functional adenoma, most of the patients had TSH-secreting adenoma i.e., 25 (21.9%), 17 (14.9%) had ACTH-secreting adenomas, 12 (10.5%) had prolactinoma and 11 (9.6%) had growth hormone (GH) secreting adenoma. The results of this study are almost similar to the study conducted by Molitch et al.⁷ Aside from the potential delay in diagnosis caused by gender differences in symptom presentation, the higher prevalence of macroadenomas among NFPA (nonfunctioning pituitary adenomas) in males compared to females leads to the hypothesis that the sex hormone profile plays an important role in predicting their biological behavior and metabolic profile. More research is needed, however, to better substantiate the impact of gender variations on the development, progression, and metabolic repercussions of NFPA.¹⁶

In the present study, most of the patients had the frequency of the type of the tumor on the size on MRI findings, 60 (52.6%) found micro adenoma and 54 (47.4%) had macro adenoma. In an almost similar study conducted by Saeger et al.¹¹ while in the frequency distribution of age with respect to types of adenoma, patients with

functional adenoma were 30 (26.3%) and with non-functional adenoma were 30 (26.3%) in the age group of 18 to 40 years while patients with functional adenoma were 35 (30.7%) and with non-functional adenoma were 19 (16.7%) in the age group of 41 to 60 years. This finding is statistically not significant at $p = 0.111$. In the present study, the frequency distribution of gender with respect to types of adenoma, patients with functional adenoma were 35 (30.7%) and with non-functional adenoma 37 (32.5%) were male while patients with functional adenoma were 30 (26.3%) and with non-functional adenoma 12 (10.5%) were female. This finding was statistically significant at $p = 0.018$. In our patients, the frequency distribution of type of the tumor on size basis on MRI findings with respect to types of adenoma, patients with functional adenoma were 50 (43.9%) and with non-functional adenoma 10 (8.8%) were found with microadenoma while patients with functional adenoma were 15 (13.2%) and with non-functional adenoma 39 (34.2%) were found with macro adenoma. This finding was statistically significant at $p = 0.000$.

This study showed the frequency distribution of duration of symptoms with respect to types of adenoma, patients with functional adenoma having a duration of symptoms below 1 year were 11 (9.6%), 1 to 3 years were 25 (21.9%), 17 (14.9%) were 4 to 6 years and 12 (10.5%) above 6 years duration of symptoms while patients with non-functional adenoma having a duration of symptoms below 1 year were 6 (5.3%), 1 to 3 years were 36 (31.6%), 4 (3.5%) were 4 to 6 years and 3 (2.6%) above 6 years duration of symptoms. This finding was statistically significant at $p = 0.002$. The radiation to pituitary adenoma that is functioning or nonfunctioning is another important treatment option, especially for those that were extensively invasive to surrounding structures and those that did not undergo complete resection due to inaccessibility or involvement of critical structures. Keeping in view

the dose to adjacent structures, radiation therapy is also helpful in restricting tumor growth.

Except for endocrine-inactive adenomas, all adenoma types tended to have a more equal gender distribution in older age groups. The biggest disparity in gender distribution appeared to correlate with the peak Occurrence of each tumor type among individuals with prolactinomas, endocrine-inactive, ACTH-releasing, and, to a lesser degree, GH-releasing adenomas. Prolactinomas were most common between the second and fifth decades of life, and endocrine-inactive adenomas were between the fourth and eighth. Adenomas that release GH, ACTH, or TSH were more uniformly distributed across the adult life span. Pituitary adenomas occur at varying rates according to age and gender. The various adenoma forms a peak in radically different age groups and has vastly different female-to-male ratios. The female-to-male ratio for a specific kind of adenoma changes dramatically with age.¹⁷

Human hyperprolactinaemia may be linked to a high prevalence of obesity, however, the basis of this relationship is unknown. The purpose of the study was to determine the link between hyperprolactinaemia and body weight in individuals with prolactin-secreting pituitary tumors. Weight gain and obesity are typically related to prolactinomas, regardless of whether there is a substantial influence on hypothalamic or pituitary function. Weight loss was observed in 70% of prolactinoma patients and 90% of male patients who had their prolactin levels adjusted in this study. We recommend that hyperprolactinaemia be included in the differential diagnosis of endocrine obesity and weight gain.¹⁸

A higher prevalence of pituitary adenoma has been confirmed through many studies while showing majority of cases represent prolactinoma. The influence of sex hormones concerning gender and age has raised a question about the pathogenesis of prolactinoma which

was highlighted by many epidemiological studies.

CONCLUSION

The early detection of pituitary adenomas would help in the implementation of early treatment that would be a more effective modality. Among all the functioning pituitary adenomas prolactinomas are the most common and can be managed well by medical therapy as the first line of treatment i.e., a dopamine agonist. Though dopamine agonist therapy of prolactinoma is typically safe and efficient, there are certain refractory instances with critical radiological and epidemiological variables that lead to poor responses, such as cavernous sinus invasion, male sex, and hereditary traits. The clinician should be aware of potential risk factors of dopaminergic drugs and keeping that in view the patient should be guided properly about the adverse effects of medication such as pericarditis or fibrosing serositis.

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Additional Information

Disclosures: Authors report no conflict of interest.

Ethical Review Board Approval: The study was conformed to the ethical review board requirements.

Human Subjects: Consent was obtained by all patients/participants in this study.

Conflicts of Interest:

In compliance with the ICMJE uniform disclosure form, all authors declare the following:

Financial Relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

Other Relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

AUTHOR CONTRIBUTIONS

Sr. No.	Author's Full Name	Intellectual Contribution to Paper in Terms of
1.	Abdul Aziz Khan	Study design, methodology, and paper writing.
2.	Junaaid Alam	Data calculation and data analysis.
3.	Muhammad Irfan-ud-Din	Interpretation of Results.
4.	Nisar Ahmad	Statistical analysis.
5.	Muhammad Idrees	Literature review.
6.	Waseef Ullah	Literature review and quality insurer.