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Clinical, Laboratory, Radiologic feature, and Treatment Outcome of Pituitary Adenoma in Tikur Anbessa Specialized Hospital, Ethiopia

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Abstract

Background: Pituitary adenomas are prevalent intracranial malignancy accounting for 6%-10% of all symptomatic intracranial tumors and reach 22.5% in autopsy studies. Pituitary adenomas can present with varied clinical manifestations that include symptoms of excessive hormone secretion, signs of hormone shortage and those related to pressure effects. Despite the common occurrences of pituitary adenomas, there is no adequate data in Ethiopia.

Objectives: This study aims to provide information on clinical, laboratory, radiologic features, and management outcomes of patients with Pituitary adenoma from 2010 to 2018 in Tikur Anbessa Specialized Hospital, Ethiopia.

Methods: A retrospective cross-sectional study was conducted among pituitary adenoma patients on follow up at endocrinology and Neurosurgery referral clinics, presented between June 2010 to June 2018. Two hundred thirty-six (236) patients with a diagnosis of pituitary adenoma were included and their chart was reviewed based on a structured questionnaire. Data entered into SPSS VERSION 22 for analysis and descriptive statistics was done. Categorical data were analyzed by the chi-squared test and continuous data were analyzed using the t-test.

Results: Out of Two hundred thirty-six (236) patients with pituitary adenoma, seventy-five percent (75%) were functional pituitary adenoma while the rest twenty-five percent (25%) was a non-functional pituitary adenoma. Among the functional adenoma, eighty-nine point three percent (89.3%) were unihormonal while the rest ten point seven percent (10.7%) were pluri-hormonal adenomas. Prolactinoma was the commonest Pituitary Adenoma subtype accounted for

58.8% followed by growth hormone-secreting adenoma which accounted for 27.2% of functional adenoma. Among patients who had control laboratory tests, serum prolactin levels normalized in about 54.4% of Prolactinoma patients treated dopamine agonists.

Conclusion: of all pituitary adenoma Cases seventy-five percent (75%) were functional pituitary adenoma while the rest twenty-five percent (25%) was a non-functional pituitary adenoma. Among the functional adenoma, prolactinoma was the commonest pituitary adenoma subtype followed by growth hormone-secreting Adenoma.

Keywords: Prolactinoma; Acromegaly; NFPAs; Macroadenoma; Microadenoma

Introduction

Background

Pituitary adenomas are common neoplastic disorders accounting for 6-10% of all symptomatic intracranial tumors [1]. The prevalence of Pituitary adenomas reaches up to 22.5% of autopsies done at the Mayo clinic [1,2]. In China, prevalence is 9.52%, in a study incorporating twelve Chinese regions [3]. Pituitary adenomas are less common in children and studies have shown a prevalence of 2.7% of all supratentorial tumors in childhood [4]. The prevalence of pituitary adenoma in an African population ranged from 16.8% to 21% in studies from different hospital units in Nigeria [5].

There is a slight male preponderance in adult patients with a male to female ratio of 1.4:1 [5]. It is known to occur between ages 2-70 years, but the peak period of occurrence is between 30-60 years [6]. Prolactinomas are the most common adenomas with a frequency of 42% in some studies [7]. In the comparison by Ezzat et al. [8] of three different autopsy series, non-secreting adenomas constituted the next most prevalent group of about 14.7% while somatotrophinomas had a prevalence of 13.2%.

Pituitary adenomas can present with varied clinical manifestations that include symptoms of excessive hormone secretion by the tumor, signs of hormone shortage by the normal pituitary gland and those related to pressure effects due to the development of the tumor mass. Tumors that expand more quickly, even if they are hormonally inactive, are more likely to cause signs of an intracranial mass. Hormonal deficiencies resulting from pituitary adenomas usually follow a

sequential loss in the order of GH, LH/FSH, TSH, ACTH, and prolactin [9]. Hypersecretion of prolactin presents with gynecomastia and hypogonadism in males and amenorrhea in females [9]. Prolactinoma can also result in a mass effect on the pituitary stalk which cuts off the inhibitory effect of dopamine on mammotrophs with resulting unregulated secretion [10]. Despite the fairly common occurrences of pituitary adenomas in the general population, there is no adequate study that emphasizes on clinical, laboratory and radiologic features and therapeutic outcomes of a pituitary tumor in Ethiopia. This is study aims retrospective evaluates clinical, laboratory, Radiologic feature, and therapeutic outcome of each type of pituitary tumor.

Statement of the problem

Pituitary adenomas are one of the common intracranial malignancies worldwide. The prevalence of pituitary adenoma in an African population ranged from 16.8% to 21% in studies from different hospital units in Nigeria and in this study there is a higher prevalence of invasive pituitary tumors in African patients [5].

In a study done in Ethiopia, analysis 42 patients with pituitary adenomas which accounted for 4.54% of endocrine patients and Prolactinoma were the most common followed by Cushing's disease and Acromegaly. The patients with Prolactinomas had a good outcome with medical treatment only [47]. And In another study on pituitary Adenomas, authors reported that 53.3% of patients were males and 46.7% were females; the most common presentations being a headache in 93.3% and visual disturbances in 86.7% [48].

Due to the importance of pituitary disorders as these tumors accounts the second commonest intracranial malignancy and as common reason of Endocrine clinic visit and higher prevalence of pituitary tumors, there is insufficient research data especially on specific subtypes of Pituitary adenomas clinical feature, laboratory, radiologic characteristics, and treatment outcome and generally, the health impact is not studied in Ethiopia and in general East Africa.

Significance of study

To the best of our knowledge, there has been only one study that mainly intended to show the magnitude of pituitary Tumors in Ethiopia which was done in 2016 G.C [47]. For the last three years, there is an increase in a patient visits to TASH because of the access to Endocrine surgery. The present study will describe pituitary tumors including plurihormonal, NFPA, invasive pituitary tumors in addition to clinicoradiologic characteristics, medical and surgical outcomes in patients with Pituitary adenomas over 10 years at TASH.

This information will assist in identifying clinical and radiologic characteristics of Pituitary adenomas as well as in planning appropriate therapy for patients.

Besides, it also helps in identifying gaps and measure the quality of care in the follow up of this patients and prepare a set of a parameter which helps in the follow up of this patients, and finally helps to install pituitary tumor Excellence center with the involvement of stakeholder; Endocrinologist, Neurosurgeon, Neuroradiologist and pathologist

Literature review

The pituitary gland consists of two parts, the anterior (adenohypophysis) and posterior (neurohypophysis) divisions, which have distinct embryonic origins and discrete functional roles. The adenohypophysis is comprised of three subregions, the pars distalis, the pars intermedia, and the pars tuberalis. It develops during embryonic life from Rathke's pouch, an endodermal region of the embryonic oral cavity [15]. The cell types in the anterior lobe of the pituitary are the somatotropes (50%) which produce GH, lactotrophs (20%) which produce prolactin, corticotropes (10%) which produce adrenocorticotropic hormone (ACTH), thyrotropes (10%) which produce thyroid-stimulating hormone (TSH) and gonadotropes (10%) which produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [15].

Anatomically the pituitary sits in a region of the skull base called the hypophyseal fossa of the sella turcica ("Turkish saddle"). Inferolaterally the pituitary is bounded by sphenoid bone and the sphenoid sinus; the pituitary is covered superiorly by dura mater (the diaphragm sellae), through which the pituitary stalk passes. Superiorly lies the optic chiasm, while the lateral walls of the sella turcica are formed by the cavernous sinuses, which contain the internal carotid artery, and cran al nerves III, IV, V1, V2, and VI [15]. The sellar region is the site of different pathological entities arising from the pituitary and adjacent anatomical structures including the brain, blood vessels, nerves, and meninges. The surgical pathology of this area requires the accurate identification of neoplastic Lesions, including pituitary adenoma and carcinoma, craniopharyngioma, neurological neoplasms, germ cell tumors, and hematological malignancies, as well as non-neoplastic lesions such as cysts, hyperplasia and in inflammatory lesions [16].

According to the 2004 WHO classification [17], Adenomas deriving from adenohypophysial parenchymal cells are classified as typical adenomas or atypical adenomas. In very rare cases, they represent pituitary carcinomas. In contrast to typical adenomas, atypical adenomas are de ned by (a) their invasiveness, (b) a Ki-67 (MiB-1) proliferation index of 3% or more, and (c) extensive nuclear staining for p53 protein [18]. A significant number of pituitary tumors, 25–55% depending on the criteria used, can show signs of invasion of the dura, bone and/or surrounding anatomical structures [19,20]. However, these so-called 'invasive' pituitary adenomas display benign behavior even in the presence of marked dural invasion and are not considered malignant by the current definition. Truly Pituitary carcinomas are characterized by the presence of metastases. The incidence accounts for 0.2% of symptomatic pituitary tumors [21,22]. The so-called 'aggressive' adenomas lie between benign adenomas and malignant pituitary carcinomas and display a rather distinct clinical behavior with marked/gross invasion of nearby anatomical structures. According to the WHO classification in 2004, endocrine pituitary tumors are clinically classified as functioning (mainly secrete adrenocorticotropic

hormone [ACTH] with Cushing's disease; growth hormone [GH] with acromegaly and prolactin [PRL] with amenorrhea – galactorrhea) and nonfunctioning (mainly–luteinizing hormone [LH] and folliclestimulating hormone [FSH]) tumors [17,26].

Incidence estimates for pituitary adenomas vary widely, suggesting the effects of numerous risk factors or varying levels of tumor surveillance. Recent studies have shown that invasive adenomas may approximately affect 1 in 1000 people of the general population [27]. Surveillance, Epidemiology, and End Results (SEER) Programs in the United States (N=8,276), observed that incidence rates generally increased with age and were higher in females in early life and higher in males in later life. Males are diagnosed with larger tumors on average than females. Diagnosis may be delayed for males, giving tumors a chance to grow larger before clinical detection. They also observed that American Blacks have higher incidence rates for pituitary adenomas compared with other ethnic groups [17]. A study from Belgium found a prevalence of clinically relevant pituitary adenomas of 94 per 100,000. Of this group, 66% were Prolactinomas, 14.7% were not endocrine-active, 13.2% had acromegaly, 5.9% had Cushing's disease, and 20.6% had hypopituitarism [29]. Meta-analysis showed that the estimated prevalence of pituitary adenomas was 14.4% in postmortem studies and 22.2% in radiological studies, with an overall estimated prevalence of 16.9% [30]. These figures contravene the conventional view of Pituitary adenomas as rare; pituitary adenomas are indeed common in the general population

The overall age-adjusted incidence rate of pituitary tumors has been reported by the Central Brain Tumor Registry of the United States (CBTRUS) as 2.94 cases per 100,000 persons [31]. After gliomas and meningiomas, tumors of the pituitary are the third most common brain tumor, accounting for 10%–15% of all primary brain tumors [32].

Symptoms of pituitary disorders are often nonspecific and may differ given the effects of space-occupying lesions, increased hormonal release or both [23]. Although most are not symptomatic, they can cause a wide array of symptoms depending on secreting can cause symptoms as a result of intracranial mass effect [24]. Considering the small size of many pituitary tumors and their tendency to exist without symptoms, estimation of their accurate prevalence of PAs is challenging. Tumors that expand more quickly, even if they are hormonally inactive, are more likely to cause signs of an intracranial mass, including visual field disturbances [25]. Among patients with pituitary adenomas, different types of headaches such as chronic, episodic migraines and unilateral headaches including primary stabbing headache, short-lasting unilateral neuralgiform headache, cluster headache, and hemicrania continua are commonly reported [33-35]. Pituitary adenomas are also associated with psychiatric disorders including hostility, anxiety, apathy, depression, emotional instability, and irritability [36,37].

Data on pituitary Magnetic Resonance Imaging (MRI) in patients with abnormal pituitary hormones in Saudi Arabia shows Hyper functioning pituitary hormones were significantly associated with positive MRI, 259 (63.2%) vs. 151 (36.8) whereas hypo functioning pituitary hormones were associated with normal MRI, 40 (81.6%) vs. 9 (18.4%)[38].

Although the treatment of pituitary adenoma depends on the size and type of tumor, surgery is the common treatment modality. Transsphenoidal adenomectomy is a method for tumor removal, though recently, endoscopic surgery has been commonly applied.

Surgical treatment is the treatment of choice for NFPA. In incidental NFPA, 10% of microadenomas and 24% of macroadenomas expand without treatment [39]. Surgical treatment is indicated in case of further growth, development of visual deficits, or hypopituitarism. MRI scans should be performed every year for the first 5 to 6 years after surgery since Recurrence cannot be detected by hormonal abnormalities.

Although Prolactinomas are the most common sub-type of pituitary tumors in population-based studies, they account for a minority of patients in surgical series. This is because of the excellent control rates achieved with the use of the dopamine agonist's bromocriptine and cabergoline. Two recent studies have added new information on surgical outcomes in patients with Prolactinomas. Kreutzer and colleagues reported on their experience in 212 patients who underwent resection of Prolactinomas from 1990 to 2005. These included patients who underwent surgery for 'non-classic indications,' i.e. cystic tumors and patients who simply preferred surgery over prolonged medical therapy. They found an overall remission rate of 42% for all tumors [28].

Acromegaly has been considered to be a rare disease, with an estimated prevalence in Europe of 30 to 70 individuals per million. However, current prevalence estimates are considerably higher [60].

The diagnosis of acromegaly should be suspected in individuals who present with the typical clinical features of Growth Hormone (GH) excess, which include an enlarged jaw (macrognathia) and enlarged hands and feet, which result in increasing shoe and glove size and the need to enlarge rings. The facial features become coarse, with enlargement of the nose and frontal bones as well as the jaw, and the teeth become spread apart. The diagnosis should also be considered when a pituitary mass is identified on an imaging study; 75 to 80 percent of somatotroph adenomas are macroadenomas at the time of diagnosis. The first step in the diagnosis is the measurement of a serum insulin-like growth factor 1 (IGF-1) concentration [61]. A normal serum IGF-1 concentration is strong evidence that the patient does not have acromegaly. If the serum IGF-1 concentration is high (or equivocal), serum GH should be measured after oral glucose administration. Inadequate suppression of serum GH after a glucose load confirms the diagnosis of acromegaly [60,61].

Thyrotropin (TSH)-secreting pituitary adenomas are rare tumors that account for less than 2% of all pituitary adenomas [40,41]. Transsphenoidal surgery is the first-line treatment for these tumors. However, most studies, even recent papers describing remission rates of 0% to 55%, report poor surgical outcomes due to relatively high frequencies of large adenomas, invasive adenomas, and/or markedly fibrous adenomas, although a steady decrease in the proportion of macroadenomas has been reported [42,43]. In some cases (e.g.

relevant tumor mass post-surgery or invasion of the cavernous sinuses), radiotherapy is recommended [44].

General objective

The main purpose of this study is to provide Data on clinical, laboratory, radiologic feature, and therapeutic outcome of Pituitary adenoma in Tikur Anbessa Specialized Hospital, Ethiopia

Specific objective:

To determine types of Pituitary Adenoma

To assess the epidemiologic characteristics of Pituitary Adenoma

To characterizes the clinical feature of Pituitary Adenoma

To evaluate radiologic finding of Pituitary Adenoma

To assess the response pattern of Pituitary Adenoma

Materials and Method

Study area

This study is conducted in the Tikur Anbessa specialized Hospital which is the largest referral hospital in the Ethiopia, with greater than 700 beds and its main teaching hospital. The TASH has 200 Doctors, 379 Nurses 115 other health professionals dedicated to providing health care services. It is characterized as one of the highly qualified centers for diagnosis and treatment of pituitary tumors in Ethiopia, and it's also the main referral center for patients with pituitary tumors, neurosurgical and Endocrine disorder from Ethiopian hospitals.

Study design

The study was a retrospective cross-sectional with a review of medical records.

Study period

The study was conducted from February 1 to April 30, 2019.

Study population

The study includes all patients with pituitary adenoma presented to Endocrinology and neurosurgery referral clinic.

Sampling method

From the appointment logbook, two hundred seventy-seven (277) consecutive patients presented between June, 2010 to June 2018 at Endocrine and neurosurgery clinics were selected and 41 patients excluded based on the exclusion criteria.

Sample size

Based on the above sampling process, two hundred thirty-six (236) patients were included in the study

Inclusion and exclusion criteria inclusion criteria:

Inclusion: All patients with pituitary Adenoma presented to Tikur Anbessa specialized Hospital that fulfills the case definition of pituitary tumors with imaging (CT scan and MRI) and/or laboratory findings.

Exclusion criteria: Patients<5 years old, those having an alternative diagnosis of a pituitary lesion, subjects entering the region from another geographical site and medical record with insufficient information.

Study variables

Dependent variable:

Cardiovascular disease

Prolactin level

Blurring of vision

Headache

Acral growth

Optic chiasm compression

Type 2 diabetes mellitus

Galactorrhea

Menstrual irregularity

Medical outcome and surgical outcome

Independent Variables:

Socio-demographic variables (sex, age, ethnicity)

Pituitary Adenoma

Functional Pituitary Adenoma

NFPA

Hypopituitarism Prolactinoma

Acromegaly

ACTH dependent Cushing disease

Microadenoma Macroadenomas giant macroadenomas

TSH dependent hyperthyroidism

Data collection

A Structured questionnaire developed after reviewing the literature, previous studies and adapted from other related researches. (Annex) was prepared. Data regarding sociodemographic characteristics, clinical features, Functionality of tumor, radiologic findings, serum level of Endocrine and Biochemical studies and treatment outcome were collected using the questionnaires.

Data quality assurance

The questionnaire was pre-tested on ten patients. The final questionnaire was revised based on the pre-test. The principal investigator was the one who collected the whole data.

Data analysis and interpretation

Each collected data was checked for quality and completeness and entered into SPSS version 22 for analysis. Descriptive statistics were used to show frequencies and tables. Categorical data were analyzed by the chi-squared test and continuous data were analyzed using the t-test. $p<0.05$ was considered as statistically significant.

Operational definitions

Acromegaly a disease that results from persistent hypersecretion of growth hormone (GH). Excess GH stimulates the hepatic secretion of insulin-like growth factor 1 (IGF-1), which causes most of the clinical manifestations.

Cushing's disease is caused by pituitary corticotropin (ACTH)-secreting tumors Galactorrhea is the discharge of milk from the breast not associated with pregnancy or lactation.

Giant Macroadenomas-pituitary tumor which is greater than 2.5 cm in diameter

Microadenoma-pituitary tumor which is less than 10 mm in diameter

Macroadenomas-pituitary tumor which is greater than or equal to 10 mm in diameter

Non-functioning pituitary tumour-A non-functioning pituitary tumor arises from pituitary cells but does not secrete clinically detectable amounts of a pituitary hormone.

Prolactinoma-PRL secreting pituitary adenoma

Prolactin-The normal serum prolactin level is less than 10 or 20 ng/mL, depending on the laboratory. Women tend to have slightly higher levels than men, probably because of the estrogen stimulation of prolactin secretion. In patients with prolactin-secreting tumors, the levels are usually higher than 100 ng/mL but maybe as low as 30 to 50 ng/mL if the tumor is small. A level greater than 100 ng/mL is almost always indicative of a prolactin-secreting tumor.

Pituitary adenomas-Pituitary adenomas are benign tumors of the anterior pituitary, but they are true neoplasms

Pituitary incidentaloma-PA serendipitously discovered by radiologic examination in the absence of endocrine manifestation.

Pituitary insufficiency (Hypopituitarism) is a syndrome characterized by one or more anterior pituitary hormone deficiencies as a result of aplasia or hypoplasia, destruction, infiltration, compression, or displacement of the hypothalamus and/or pituitary gland

The response is at least a 30% decrease in the sum of diameters of viable (enhancing) target lesions, taking as reference the baseline sum of the target lesions (Response Evaluation Criteria in Solid Tumor) or Normalization of laboratory control

TSH-mediated hyperthyroidism-Hyperthyroidism caused by increased thyroid-stimulating hormone (TSH) production is rare.

Radiological-operative classification of pituitary adenomas [41].

Grade 0: Enclosed adenoma with normal intact sella

Grade 1: Enclosed (intrasellar) Microadenoma with minor bulging of the sella

Grade 2: Enclosed macroadenomas, generalized sellar enlargement

Grade 3: Macroadenomas, focal sellar invasion

Grade 4: Macroadenomas, generalized sellar invasion

Larger or more extensive tumors beyond grade 3 and 4 are sub-classified as follows:

Suprasellar or symmetrical extension

10 mm-fills the chiasmatic cistern

20 mm-lifts the recesses of the third ventricle

>30 mm-fills the anterior third ventricle

Para sellar or asymmetrical extension

Extends intracranially

Lateral extension outward from the cavernous sinus

Ethical consideration

Ethical clearance was obtained from the Department of Internal Medicine and Research and Publications Committee of the School of Medicine, College of Health Sciences, and Addis Ababa University.

Dissemination of the result

The study finding will be presented for defense. The results of the study will also be sent for reputable journals for publication.

Results

A total of 236 patients with pituitary adenoma were included in this study. The median age is 32 years with IQR of 25 to 40 years. The male and female proportions are 56.8% and 43.2%, respectively. The duration of the chief complaint was within one year in 35.5% one to ten years in 59%, and above ten years in 5.6% (**Table 1)**. We have found the median duration of the chief complaint before the diagnosis of Pituitary adenoma is 2.9 years. The majority of the patients (88.1%) had an insidious onset of the symptoms (Table 2). Thirty five point five percent (35.5%) of them diagnosed within one year, one to ten years in 59%, and above ten years in 5.6%. The majority of the patients (88.1%) had an insidious onset of the symptoms.

Table 1: Background characteristics of the study participants.

Socio-demographic characteristics of the study participants			
		N	%
Sex	F	134	56.80%
	M	102	43.20%

Residence	Rural	61	26%
	Urban	175	74%
Region	Addis Ababa	116	49.10%
	Oromia	73	30.70%
	Amhara	21	8.80%
	SNNP	14	5.90%
	Afar	6	2.50%
	Tigray	6	2.50%

Table 2: The duration and onset of symptoms in patients with PA.

The duration and onset of symptoms in patients with PA			
		N	**%**
Duration	<6 m	57	24.40%
	6-12 m	26	11.10%
	1-5 y	96	41.00%
	5-10 y	42	17.9
	>10 y	13	5.60%
Onset	Acute	22	7.30%
	Incidental	16	4.60%
	Insidious	198	88.10%

The most common symptom at the time of presentation was a headache which was present in 75% of the patients. The second most common symptom was blurring of vision which was present in 57.2% of the patients. The other symptoms were a menstrual irregularity in 44%, galactorrhea in 22% growth of face, feet, and hands in 15%, and Amenorrhea 12.4%. The frequency of the other symptoms is presented in the **Table 3** below.

Table 3: Clinical presentations of patients with pituitary adenoma.

Symptoms			Less frequent symptoms		
	N	**%**		**N**	**%**
Headache	177	75.00 %	Buffalo hump	19	8.10 %
Blurred/double vision	135	57.20 %	Snoring	17	7.20 %
Menstrual irregularities	60	44%	Unexplained weight gain	16	6.80 %
Galactorrhea	52	22.00 %	Hoarseness of voice	13	5.50 %
Acral growth	37	15%	Moon face	10	4.20 %
Amenorrhea	30	12.70 %	Infertility	10	4.40 %
Back pain	29	12.30 %	Memory loss	6	2.50 %
Loss of libido	27	11.40 %	Tremor	4	1.70 %

The most common associated comorbidity was hypertension which was identified in 23.7% of the patients. About 15.7% had diabetes mellitus. Among the cardiac complications, LVH was identified in 12.7%. Heart failure in 8.5%, atrial fibrillation in 6.8% and primary Hyperthyroidism in 2.5% of the patients as shown in Table 4.

Table 4: Comorbidities in patients with pituitary adenoma.

Complications in patients with pituitary adenoma		
	N	**%**
Diabetes mellitus (Type 2)	37	15.70%
Hypertension	56	23.70%
LVH	30	12.70%
Heart failure	20	8.50%
atrial fibrillation	16	6.80%
Hyperthyroidism(primary)	6	2.50%

Of the total pituitary adenoma cases, 75% were functional pituitary adenoma while the rest 25% was a non-functional pituitary adenoma. Among the functional adenoma, 89.3% were unihormonal while the rest 10.7% were plurihormonal adenomas **(Table 5)**.

The most common functional pituitary adenoma was prolactinoma (58.8%). The second most common functional adenoma was growth hormone-secreting adenoma which accounted for 27.2% of functional adenoma. ACTH and TSH secreting adenomas accounted for 11.3% and 2.5% of functional pituitary adenomas respectively **(Table 6)**.

Table 5: Classification of the pituitary adenoma.

Functional classification of the pituitary adenoma			
		N	**%**
Functionality	FPA	177	75.00%
	NFPA	59	25.00%
FPA	Uni-hormonal	158	89.20%
	Pluri-hormonal	19	10.70%

Table 6: Sub-types of FPA.

Sub-types of FPA		
	N	**%**
Prolactinoma	93	58.80%
Acromegaly	43	27.20%
ACTH secreting PA	18	11.30%

TSH secreting PA	4	2.50%

The most common Plurihormonal pituitary adenoma was (prolactinoma and GH) Secreting Pituitary adenoma occurred (68%), (ACTH and TSH), (prolactinoma and ACTH), (Acromegaly and ACTH) secreting Pituitary adenomas each accounted 10.5% **(Table 7)**.

Out of fifty-nine (59) cases with NFPA, fifteen percent (15%) of them had hypopituitarism **(Table 8)**.

Table 7: The distribution of subtypes of PA as unihormonal and plurihormonal.

Plurihormonal	Number of patient	Percentage (%)
Acromegaly and prolactinoma	13	68%
ACTH and TSH secreting Pituitary adenomas	2	10.50%
prolactinoma and ACTH secreting Pituitary adenomas	2	10.50%
Acromegaly and ACTH secreting Pituitary adenomas	2	10.50%

Table 8: Secretory function of Nonfunctional Pituitary adenomas.

Secretory function of Non-functional Pituitary adenomas			
		Number	%
NFPA	Hypopituitarism	9	15%
	Normal secretory function	50	85%

The majority (64.7%) of the patients had macroadenoma and 35.3% had microadenoma **(Table 9).** On brain imaging, 98.3% of the patients had pituitary tumors. On imaging, features that suggest invasive PA were identified as a significant proportion of the patients. Compression of the optic chiasm was present in 56.4%, diaphragmatic Sella abnormality in 43.2%, infundibulum abnormality of the in 35.5%, sellar floor erosion in 19.9%, and invasion of the cavernous sinus was present in 13.6% of the patients.

The median tumor size at presentation was 18 mm. The observed minimum and maximum tumor sizes were 5 mm and 86 mm, respectively. About 20% of the patients had a tumor size of greater 4 cm at presentation **(Tables 10-12)**.

Table 9: Size category of the pituitary adenoma.

Size category of the pituitary adenoma			
		N	%
Size	Microadenoma	80	34.40%
	Macroadenoma	152	65.50%

Table 10: Tumor size of the pituitary adenomas.

Tumor size of the pituitary adenomas			
		N	%
Size	<10	83	35.30%
	20-Oct	44	18.70%
	21-30	48	20.40%
	31-40	14	6.00%
	41-50	29	12.30%
	>50	17	7.20%

Table 11: Imaging findings in patients with pituitary adenoma.

	CT scan	MRI	Total	Overall%
Focal lesion	22	210	232	98.30%
Empty sella	o	4	4	1.70%
Sellar floor erosion	6	41	47	19.90%
Diaghramatic sella abnormality	8	94	102	43.20%
Infundibulum abnormality	6	77	83	35.50%
Cavernous sinus invasion	4	28	32	13.60%
Optic chiasm compression	10	123	133	56.40%

Table 12: Radiologic grades of the PA.

Radiologic grades of the PA			
		N	%
Radiologic grade	0	12	5.10%
	1	72	30.80%
	2	89	38.00%
	3	29	12.40%
	4	32	13.70%
Grade 3 and 4 sub classification	A	20	40.80%
	B	17	34.60%
	C	2	4%
	D	7	14.20%
	E	3	6%

Overall, 72.2% were on treatment. Of this, 62.7% were on medical treatment and 37.3% were on surgical treatment **(Table 13)**. The types of the drugs used for medical management were Bromocriptine (74%) and cabergoline (18%).

Table 13: Treatment modalities of patients with PA.

Treatment modalities of patients with PA			
		N	%

Treatment category	Medical	116	62.70%
	Surgical	69	37.30%
Medical treatment	Bromocriptine	86	74%
	Cabergoline	21	18%
	Hormone replacement and AVP	9	7.60%
Surgical approach	Transsphenoidal	58	84%
	Craniotomy	11	26%

Treatment response for medically managed patients was assessed for prolactinoma. About 54% of the patients with prolactinoma who were treated medically had normalization of the prolactin level **(Table 14)**. Among the patients who were managed surgically, the tumor was cleared in 71.1%, decreased by more than 30% was 10.4%, and less than 30% was 18.6%, requiring a second surgery. Of the patients who had laboratory control tests after surgery, 20.9% developed hypopituitarism **(Tables 15 and 16)**.

Table 14: Treatment response of patients with prolactinoma managed medically.

Treatment response of patients with prolactinoma managed medically.			
Response (prolactinoma)	Normal PRL	43	54.40%
	High	36	45.60%

Table 15: Imaging findings after the pituitary surgery.

Imaging findings after the pituitary surgery			
		N	**%**
Control image after surgery	Cleared	49	71%
	More than 30%decrement	7	10.40%
	Less than 30%	13	18.60%

Table 16: Laboratory results after the surgery.

Laboratory results after the surgery			
		N	**%**
Lab control after surgery	Hypopituitarism	8	21.10%
	Normalize	30	78.90%

Among functional Pituitary adenoma, females are predominant accounts 61.9% and in NFPA males account for a higher proportion of 62.8%. Headache and blurring of vision occurred 73.6% and 48.7% respectively in FPA. Headache occurred 81.4% and blurring of vision 95.3% NFPA. Besides, we observed a higher proportion of invasive NFPA was seen compared to FPA **(Tables 17-19)**.

Plurihormonal PA observed with higher invasive disease and mean diameter (25 mm) compared to unihormonal PA 18 mm.

Table 17: Comparison of characters among FPA and NFPA.

		FPA		**NFPA**		
		N	**%**	**N**	**%**	**p value**
Sex	F	117	61.90%	16	37.20%	0.003
	M	72	38.10%	27	62.80%	
Headache		142	73.60%	35	81.40%	0.284
Blurring of vision		94	48.70%	41	95.30%	0

Table 18: Comparison of radiologic findings in unihormonal and plurihormonal PA.

Comparison of radiologic findings among FPA and NFPA					
	FPA		**NFPA**		
	N	**%**	**N**	**%**	**p value**
Sellar floor erosion	26	13.50 %	21	48.80 %	<0.0001
Diaghramatic sella abnormality	68	35.20 %	34	98.40 %	<0.0001
Infundibulum abnormality	48	25.10 %	35	79.10 %	<0.0001
Cavernous Sinus Invasion	12	6.20%	20	46.50 %	<0.0001
Optic Chiasm Compression	92	47.70 %	41	95.30 %	<0.0001
Size (mean, mm)	19		37		<0.0001

Table 19: Comparison of radiologic findings in unihormonal and plurihormonal PA.

	Unihormonal		**Plurihormonal**		
	N	**%**	**N**	**%**	**p value**
Sellar floor erosion	21	13.20 %	5	26.30%	0.306
Diaghramatic sellae abnormality	52	32.90 %	13	68.40%	0.036
Infundibulum abnormality	34	21.50 %	8	42.10%	0.194
Cavernous Sinus Invasion	12	7.50%	0	0.00%	0.166
Optic Chiasm Compression	70	44.30 %	15	78.90%	0.774
Size (mean, mm)	18		25		0.123

Prolactinoma and ACTH dependent tumors were observed predominantly among female participants while, Acromegaly occurred more frequently among male participants. Among the comorbidities, both hypertension and diabetes occurred more frequently in patients with ACTH dependent tumors and

Acromegaly. Both were observed less frequently in patients with Prolactinoma.

Cardiac comorbidities were also observed more frequently in patients with ACTH dependent tumors and Acromegaly. No patient with Prolactinoma had evidence of cardiac dysfunctions **(Table 20)**.

Table 20: Symptoms more specific to a certain tumor type.

		Prolactinoma		Acromegaly		ACTH tumor	
		N	%	N	%	N	%
Sex	F	71	76.30 %	18	41.90 %	17	89.50 %
	M	22	23.60 %	25	58.10 %	2	10.50 %
Duration	<6 m	17	18.20 %	0	0.00%	4	21.10 %
	6-12 m	13	13.90 %	2	4.70%	0	0.00 %
	1-5 yr	39	41%	24	55.80 %	11	57.86 %
	5-10 yr	20	21.40 %	12	27.90 %	4	21.04 %
	>10 yr	4	4.30%	5	11.60 %	0	0.00 %
	Hypertension	5	5.30%	15	34.90 %	12	63.20 %
Comorbiditis	Diabetes	3	3.30%	22	51.20 %	4	21.10 %
	LVH	4	4.30%	8	18.60 %	6	31.60 %
	Heart failure	-	-	8	18.60 %	2	10.50 %
	Arrhythmia	-	-	4	9.30%	4	21.10 %
	Hyperthyroidism (primary)	-	-	6	13%	-	-

Headache and blurring of vision were the most common clinical symptoms at presentation. Both were most commonly observed among patients with Acromegaly. The blurring of vision was relatively less common in patients with ACTH dependent tumors **(Table 21)**. The blurring of vision was significantly associated with tumor size, optic chiasm compression, and radiologic grade of the tumor. The mean size of the tumors in patients with a blurring of vision was 30 mm compared to 10 mm in patients without blurring of vision. Therefore, increased tumor size associated with supra-sellar extension will increase the risk of optic chiasm compression that in turn causes visual dysfunction and irreversible blindness if not intervened timely **(Table 22)**.

Table 21: Headache, Blurring of Vision: Symptoms more specific to a certain tumor type.

	Headache		Blurring of vision	
	N	%	N	%
Prolactinoma	63	67.70%	44	47.10%
Acromegaly	38	88.40%	27	62.80%
ACTH dependent tumors	13	68.40%	6	31.60%

Table 22: Association of blurring of vision and radiologic grade.

Shows association of blurring of vision and radiologic grade						
		Blurring of vision				
		No		Yes		
		N	Percentage (%)	N	Percentage (%)	p value
Optic chiasm compression	No	81	78.60%	22	21.40%	<0.0001
	Yes	20	15.00%	113	85.00%	
	2	29	32.60%	60	67.40%	
	3	2	6.90%	27	93.10%	
	4	0	0.00%	32	100.00%	
Tumor size (mean, mm)	10.2			30.7		<0.0001

The most common tumor-specific symptom among Prolactinoma patients were menstrual irregularities and Galactorrhea. Galactorrhea occurred more frequently in females but it was also observed in male patients with Prolactinoma **(Tables 23 and 24)**. Among the patients with Acromegaly, growth of the face, hands, and feet occurred in 83.7% of patients, and was the commonest tumor-specific symptom in these groups of patients. Buffalo hump was the commonest manifestation of Cushing syndrome in patients with ACTH dependent tumors.

Table 23: Symptoms more specific to a certain tumor type.

Symptoms more specific to a certain tumor type			
		N	%
Prolactinoma	Menstrual irregularities	49	69%
	Galactorrhea	45	48.20%
	Amenorrhea	23	32%
	Loss of libido	17	18.80%
Acromegaly	Acral growth	36	83.20%
	Hoarseness of voice	9	20.90%

ACTH	Buffalo hump	15	78.90%
	Moon face	8	42.10%
	Hyperpigmentation	7	36.80%

Table 24: Galactorrhea.

Galactorrhea					
		No		Yes	
		N	%	N	%
Sex	F	29	45.30%	35	54.70%
	M	16	84.20%	3	15.70%

The mean tumor size was largest in patients with Acromegaly and was smallest in patients with ACTH dependent tumors **(Table 25)**. The compression of the optic chiasm was observed most frequently in patients with Acromegaly.

Table 25: Comparison of radiologic findings in different types of pituitary adenoma.

Comparison of radiologic findings in different types of pituitary adenoma						
	Prolactinoma		Acromegaly		ACTH dependent	
	N	%	N	%	N	%
Sellar floor erosion	15	16.10%	3	7.00%	2	10.50%
Diaghramatic sellae abnormality	29	31.10%	14	32.60%	6	31.60%
Infundibulum abnormality	14	15%	12	27.90%	4	23.50%
Cavernous Sinus Invasion	10	10.70%	2	4.70%	2	10.50%
Optic Chiasm Compression	38	40.80%	25	58.10%	2	10.50%
Size (mean, mm)	18		20		14	

The baseline serum prolactin level in the prolactinoma patient **(Figure 1)** ranges from 64 to 8909 ng/ml, the mean value is 1266 ng/ml and median 563 ng/ml and has an association with tumor size.

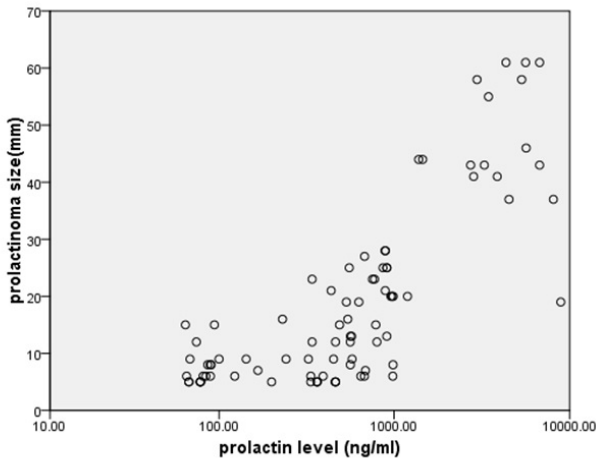

Figure 1: Scatter plot, demonstrating an association of prolactin level and Prolactinoma size.

Of all Acromegaly patients, 44.1% were treated by surgery and 34.8% were treated with a dopamine agonist. Among the patients with ACTH dependent tumors, 77% treated surgically. The remaining patients are not on treatment **(Table 26).**

All patients with Uni-hormonal Prolactinoma received medical treatment **(Table 27).** ***About 79.5% of these patients were treated with Bromocriptine and the rest 20.5% were treated by Cabergoline.***

The median dose of Bromocriptine is 2.5 mg/d (ranges from 2.5 mg to 20 mg).

All patients on cabergoline were on 2.5 mg PO two times per week.

Table 26: Treatment category of patients with pituitary adenoma.

Treatment group				
	Medical		Surgical	
	N	%	N	%
Prolactinoma	93	100.00%	0	0.00%
Acromegaly	15	34.80%	19	44.10%
ACTH dependent			14	77%

Table 27: Medical treatment of patients with Prolactinoma.

Medical treatment of patients with Prolactinoma			
		N	%
Drug type	Bromocriptine	74	79.50%
	Cabergoline	19	20.50%

Treatment response was assessed for patients with Prolactinoma **(Tables 28 and 29)**. Among the patients who had

at least a single laboratory control after 6 months of treatment was 84%, the prolactin level normalized in about 54.4%. Larger tumor size at presentation was associated with less response to medical treatment in patients with Prolactinoma.

Table 28: Response to drug.

Response to Drug		N	%
Response (PRL)	Normalized(20 ng/ml)	43	54.40%
	Decreased(20-50 ng/ml)	10	12.60%
	More than 50 ng/ml	26	33%

Table 29: Association of tumor size with treatment response in patients with Prolactinoma.

	Response	N	Mean	p value
Mean tumor size	Normal to Decreased(o-50 ng/ml)	43	15.32	0.01
	More than 50 ng/ml	36	23.72	

Discussion

In this retrospective study, the mean age of presentation is 32 with IQR of 25 to 40 years. The male and female proportions are 56.8% and 43.2%, respectively.

Among functional Pituitary adenoma, female accounts 61.9% and in nonfunctional Pituitary adenoma males account 62.8%. The sex ratio is consistent with other studies done US [27]. But the mean age is younger when compared to other studies [27]. In Israel, a populationbased study from 1960–1966, reported the highest incidence of Pituitary adenoma in the 40–69 year age group [54]. We believe this is because the majority of the Ethiopian population is younger. The median age group of the Ethiopian population is 18.6 years.

We have found the median duration of the chief complaint before a diagnosis of Pituitary adenoma is 2.9 years and only 35.5% of a patient diagnosed within a year. This tumor can be easily missed because of relatively low incidence, nonspecific symptoms of pituitary adenoma and requires cross-sectional imaging and laboratory facility which are not widely available in Ethiopia.

Of the total 236 pituitary adenoma cases, seventy-five (75%) were functional pituitary adenoma while the rest 25% was a non-functional pituitary adenoma. Among the functional adenoma, 89.3% were unihormonal while the rest 10.7% were pluri-hormonal adenomas. A similar finding of (30 to 35 percent) clinically nonfunctioning pituitary adenoma was reported [54, 62].

According to the present result, the most common subtype of pituitary adenoma was prolactinoma (58.8%). Followed by Acromegaly which accounted for 27.2% of functional adenoma. ACTH and TSH secreting adenomas accounted for 11.3% and 2.5% of functional pituitary adenomas respectively. Similar findings observed in several studies. Gruppetta et al. [54] reported that the most common subtypes of pituitary adenoma were Prolactinomas (46.2%), NFPA (34.2%) and GHsecreting adenomas (16.5%).

Overall the most common symptom at the time of presentation was a headache which was present in 75% of the patients followed by blurring of vision in 57.2% of the patients. Headache and blurring of vision occurred 73.6% and 48.7% of functional pituitary adenoma respectively and 81.4% and 95.3% nonfunctional pituitary adenoma respectively. In line with our study, Gruppetta et al. [54] reported that the most common presenting feature in pituitary adenoma was a headache, approximately 40% of cases, followed by visual impairment.

In the present study majority of patients had macroadenoma 64.7% and 35.3% had microadenoma. On brain imaging, 98.3% of the patients had focal lesion and the remaining had empty sella. Imaging features that suggest Invasive pituitary adenoma was identified as a significant proportion of the patients. Compression of the optic chiasm was present in 56.4%, infundibulum abnormality in 35.5%, abnormality of the diaphragmatic sella 43.2%, sellar floor erosion in 19.9%, and invasion of the cavernous sinus was present in 13.6% of the patients. Besides, we observed a higher proportion of invasive nonfunctional pituitary adenoma was seen compared to functional pituitary adenoma. A similar finding of a higher prevalence of invasive pituitary adenoma reported in Nigerian study [5].

The median tumor size at presentation was 18 mm. The observed minimum and maximum tumor sizes were 5 mm and 86 mm, respectively. About 20% of the patients had tumor size of more than 4 mm at presentation

There was an apparent correlation between blurring of vision and tumor size, optic chiasm compression, and radiologic grade of the tumor. The mean size of the tumors in patients with a blurring of vision was 30 mm compared to 10 mm in patients without blurring of vision. Therefore, increased tumor size associated with supra-sellar extension will increase the risk of optic chiasm compression that in turn causes visual dysfunction and irreversible blindness if not intervened timely.

There is an important difference between prolactinoma cases by sex and age. The female-to-male ratio was 3.4: 1. The median age of prolactinoma was 29 years for females and 36 years for males. A similar evaluation in Iceland found a discrepancy between sexes, with a median peak in incidence that was significantly younger in women than in men (32 versus 47 years of age, respectively). The results of the current study confirmed that the PRL level showed a good correlation with tumor size; and male patients had significantly higher PRL levels and larger adenomas [55,57,58].

The most common tumor-specific symptom among Prolactinoma patients were menstrual irregularities (52.9%) and Galactorrhea (48.2%). Galactorrhea occurred more frequently in females but it was also observed in male patients. Galactorrhea and amenorrhea are sensitive indicators of PRL excess, so female patients of reproductive age seek medical assistance earlier than male and older female patients who lack such endocrine signs

[56]. Estradiol is a known sex steroid which induces PRL cell hyperplasia and PRL-producing tumor formation in the pituitary gland. These physiologic effects of estradiol may affect the unique proliferative activity of female prolactinoma.

All patients with Prolactinoma received medical treatment. About 79.5% of these patients were treated with Bromocriptine and the rest 20.5% were treated with Cabergoline. Among patients who had control laboratory tests, the prolactin level normalized in about 54.4% of patients treated with a dopamine agonist. We have found that the median diameter was 15.32 mm in those who achieved normal prolactin and 23.7 mm in those who failed to achieve normal prolactin. According to other studies, approximately 70 percent of patients achieved normal prolactin concentrations following dopamine agonist [57]. Because of large pituitary tumor and lower doses of a dopamine agonist in our study resulted in a lower proportion of Prolactinoma with normal serum prolactin level. There is no report of dopamine agonist related valvular heart disease

In this study Acromegaly accounts for 26.2% of pituitary adenoma with a female to male ratio of 1:1.5. We found out Growth of the face, hands, and feet occurred in 83.7% and were the commonest tumor-specific symptom in these groups. We observed the higher proportion of acromegaly patients had various comorbid conditions include Hypertension occurred 34.9%, Diabetes 51.2%, LVH and Heart failure 18.6%, atrial fibrillation 9.3% and primary hyperthyroidism 13%. Similarly, a greater number of comorbidities were observed in a single-center registry in biochemically uncontrolled patients with Acromegaly compared to their controlled counterparts. They found

Comorbidities were typically more prevalent in uncontrolled versus controlled patients-24 (58.5%) vs. 33 (41.8%) had hypertension, 17 (41.5%) vs. 20 (25.3%) had diabetes, 11 (26.8%) vs. 16 (20.3%) had sleep apnea, and 3 (7.3%) vs. 3 (3.8%) had cardiomyopathy [59].

We demonstrated a greater number of GH producing tumors were mostly macroadenomas (76%) and the mean tumor size was 20 mm. similar data was available with other studies, GH producing tumors were Macro adenoma 93 patients (87.7%) and microadenomas in 13 patients (12.3%) [59].

Conclusion

The data collected in our study provided an overview of the patients with Pituitary adenoma. Overall seventy-five (75%) were functional pituitary adenoma while the rest twenty-five (25%) was a non-functional pituitary adenoma. Among the functional adenoma, prolactinoma was the commonest Pituitary adenoma subtype followed by growth hormone secreting adenoma.

Limitation of study

Since this study was a retrospective investigation, the obtained data were incomplete in medical files and a significant number of the patient do not have regular laboratory and imaging follow up per recommendation. Data about immunohistochemistry was not available in patients who underwent surgery, and we recommend these matters be considered in future studies.

Recommendations

We recommend the Hospital to develop an evidence-based computerized database of pituitary tumor registry to define features of prognostic significance and prospective clinical studies needed to assess the outcome of treatment of the different pituitary lesions.

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