

ADDIS ABABA UNIVERSITY
COLLEGE OF HEALTH SCIENCES
DEPARTMENT OF INTERNAL MEDICINE



RESEARCH TITLE

CLINICAL CHARACTERISTICS, DIAGNOSIS AND TREATMENT RESPONSE OF ADULT PROLACTINOMA PATIENTS ON FOLLOW UP AT ENDOCRINE CLINIC OF TIKUR ANBESSA SPECIALIZED HOSPITAL

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SUMMARY PAGE

PROJECT TITLE

Clinical characteristics, diagnosis and treatment response of adult prolactinoma patients on follow up at endocrine clinic of TikurAnbessa Specialized Hospital during the period from June 2015 to June2020, Addis Ababa, Ethiopia.

THEMATIC AREA: Endocrinology

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3. FILL TITLE OF THE PROJECT

Clinical characteristics, diagnosis and treatment response of adult prolactinoma patients on follow up at endocrine clinic of TikurAnbessa Specialized Hospital during the period from June 2015 to June2020, Addis Ababa, Ethiopia.

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Abstract

BACKGROUND- Prolactinomas are the most common type of pituitary adenomas in both sexes with different age distribution. They are benign neoplasms accounting for approximately 40% of all pituitary tumors. They are classified into two main groups based on the size of pituitary tumour at presentation: microprolactinoma (tumour diameter <1 cm) and macroprolactinoma (tumour diameter >1 cm). The clinical presentation of prolactinoma includes manifestations relating to hyperprolactinaemia and features relating to tumor bulk.

OBJECTIVE- The objective of this study is to assess the clinical profile, diagnosis and treatment response of patients with prolactinoma on follow up at endocrine clinic of Tikur Anbessa specialized Hospital (TASH).

METHOD; A hospital based retrospective cross sectional study was conducted on adult patients with confirmed prolactinoma attending Endocrine clinic of TASH from June, 2015 to June 2020. All patients with prolactinoma on follow up at endocrine clinic of TASH on the stated period were included. Data collection was conducted by the principal investigator from the charts and electronic medical records of patients using a structured questionnaire. Data was cleared and entered to IBM SPSS version 26. Result was processed and analyzed using SPSS version 26. Descriptive statistics were used as a statistical data analysis method and presented as frequencies and percentages with their corresponding confidence intervals. Logistic regression analysis was used to assess the association between initial tumor size and prolactin level and a P value of <0.05 was considered significant.

Result: Among the 217 patients with pituitary adenoma, prevalence of prolactinoma was 91 (41.9%). 76.8% patients with prolactinoma were females. The mean age was 30.78 years (SD ± 7.97). Headache was the major presenting symptom (68.1%) followed by visual disturbance (49.3%). Most patients (79.7%) had macroadenoma. PRL level was <250 ng/ml in 54.71% females and >500 ng/ml in 56.25% males. 67 out of the 69 patients were treated (medical and/or surgical). 59 (85.5%) patients had clinical response and 10 (14.5%) had no clinical response. On multivariate logistic regression the prolactin level has strong association with the initial tumor size with p value <0.003, AOR of 19.51, 95% CI (2.689, 141.6). Treatment was discontinued in 16 out of the 65 patients and disease remission and financial limitation were the major reasons.

Conclusion: Prolactinomas are the most common secretory pituitary tumors accounting for 41.9%. The initial tumor size has association with the presenting symptom and initial prolactin level. Our Patients with prolactinoma has good clinical response to medical therapy

Recommendation- Laboratory investigations of hormonal analysis, MRI and drugs (dopamine agonists) should be available in the hospital.

Key words- prolactinoma, TASH, prolactinoma, medical therapy, dopamine agonists

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Abbreviations and acronyms

TASH-	TikurAnbessa Specialized hospital
DAs-	dopamine agonists
AAU-	Addis Ababa University
PRL-	Prolactin
SSA-	Sub Saharan Africa
IBM-	international business machines
SPSS-	statistical package for the social sciences

INTRODUCTION

Background

Sellar tumors account for 10-15% of all intracranial neoplasms. pituitary adenomas and craniopharyngiomas are the most common types, accounting for 58-80 % of the lesions.¹

Prolactinomas are the most common type of pituitary adenomas in both sexes.² Prolactinomas are benign neoplasms accounting for 40% of all pituitary tumors.³ They are broadly classified as microprolactinoma (tumor diameter <1 cm) and macroprolactinoma (tumor diameter >1 cm).⁴

Hyperprolactinemia is the most common pituitary disorder which can be caused by physiological, pharmacological or pathologic factors.⁵

From a study done in Nigeria there is a trend of increment of hyperprolactinemia with a prevalence of 31.7% among females with infertility.⁶

Normal PRL levels in men and women are usually taken 20 and 25 µg/l, respectively.³

According to the endocrine society clinical practice guideline, February 2011, the diagnosis of hyperprolactinemia is established with a single measurement of serum prolactin; a level above the upper limit of normal confirms the diagnosis with proper sample collection. A prolactin level greater than 500 µg/liter is diagnostic of a macroprolactinoma.⁷

Dopamine agonists (DA), cabergoline and bromocriptine are the first line of therapy for patients with macroprolactinomas. These drugs inhibit prolactin secretion and reduce tumor volume.⁸

Trans-sphenoidal pituitary surgery remains an option when primary medical DA therapy is not effective or not well tolerated.⁴

Statement of the problem

Prolactinomas are the most prevalent pituitary adenomas, accounting for 45–66% of all pituitary adenomas, with an estimated prevalence of 62 cases per 100,000 individuals.⁸

Hyperprolactinemia is one of the most frequent disorders of the pituitary gland. It is responsible for 20 to 25% of consultations of secondary amenorrhea and 17% for female infertility, and can be caused by physiological, pharmacological or pathologic factors. Patients may be managed by different specialists in the Middle East and North Africa (MENA) region and no data exist on patterns of clinical management.⁹

There is paucity of data concerning sub-Saharan Africa (SSA).⁵

Although there is a study on pituitary lesions, there is no study done on prolactinoma in Ethiopia.

Significance of the study

This study is the first of its kind for the nation and for the institution and it will have an impact in the field of endocrinology in assessing the clinical characteristic, diagnosis and treatment outcome of adult patients with prolactinoma. Additionally it will have contribution to fill the gap in the approach of patients with initial presentation of symptoms related to gynecologic issue like infertility that have follow-up to gynecologic clinics without timely diagnosis and proper treatment.

LITRATURE REVIEW

Burden of the disease

Pituitary adenomas are the most common tumours occurring in the sellar area constituting for 10 to 15% of all intracranial tumors. They are either clinically functioning adenomas or non-functioning adenomas.^[10, 11] Prolactinoma is the most common benign functional pituitary tumor. It accounts for about 40-60% of functional pituitary tumors.¹² Hyperprolactinemia is the most common disorder involving the hypothalamic-pituitary axis, responsible for about 20% of secondary amenorrhea and 17% of infertility consultation.^[5, 9]

Epidemiology

Socio demographic characteristic of patients with prolactinoma

In a clinical records of 56 patients with nonpuerperal galactorrhea and/or hyperprolactinemia at Winnipeg, Manitoba, Canada, the median age of the 56 patients was **26** years (range 17 to 41 years) at the time of the initial visit.¹³

In a prospective study of 76 consecutive infertile women in sub-Saharan Africa, Nigeria, the mean age of the patients was 33.4 years with a range of 22 to 43 years.⁶

Majority of the patients with prolactinoma are young, female patients.^(14, 5, 8, 11)

Causes

Hyperprolactinemia is the most common pituitary disorder which can be caused by physiological, pharmacological or pathologic factors.⁵

Some of the physiological causes are pregnancy, breast-feeding, stress, exercise. Among the pathologic systemic causes of moderate hyperprolactinemia renal insufficiency is the commonest one, which is mainly due to impaired renal degradation and clearance of prolactin and enhanced production of the hormone. Patients with renal insufficiency and hyperprolactinoma will have improvement of their prolactin level after renal transplantation but dialysis has no effect on serum prolactin level.⁷

Clinical profile of patients with prolactinoma

The clinical presentation of prolactinoma includes manifestations relating to hyperprolactinaemia including galactorrhea, reduced fertility and sex-specific manifestations (menstrual disturbance

in women and erectile problems in men) and features relating to tumour bulk including visual disturbance and headache.⁴

Macroprolactinomas (defined by a diameter >1 cm) are present in only ~10% of the patients with a prolactinoma. Macroprolactinomas may present with visual field defects and headache due to mass effects of the tumor in both men and women, and with hyperprolactinemia related symptoms like amenorrhea and galactorrhea in premenopausal women. In some cases, macroprolactinomas are found as incidentalomas⁸

In clinical records of 56 patients with nonpuerperal galactorrhea and/or hyperprolactinemia after a two month to six year followup period in University of Manitoba and the Endocrine-Metabolic Unit, Health Sciences Centre, Winnipeg, Manitoba, Canada, galactorrhea was present in 52 of the 56 patients. Galactorrhea plus amenorrhea or oligomenorrhea was found in 45 patients, but in 12 of them, the milky breast discharge became evident only on physical examination (manual expression): this was termed “nonspontaneous galactorrhea.” Of the 33 patients with the presenting complaints of amenorrhea or oligomenorrhea and galactorrhea, the symptoms appeared at about the same time in 17 patients; in 16, either the amenorrhea (eight patients) or the galactorrhea (eight patients) occurred first (from four to 108 and from three to 48 months, respectively). Abnormal physical findings, except for galactorrhea, were unusual.¹³

In a cross-sectional study over a period of 2 years in a Cameroonian population done in University of Douala, Douala, Cameroon, January 2020, which included 24 females and 1 male patient, Clinical features at presentation included mainly infertility (20/25), galactorrhea (18/25), menstrual disturbances (16/24), visual defects (4/25), and erectile dysfunction in the only male patient. The most probable causes of hyperprolactinaemia were microadenoma in 13/25, macroprolactinoma in 4/25, non-secreting macroadenoma in 4/25. No cause was identified in 4/25 cases suggesting missed microadenoma or idiopathic hyperprolactinaemia.⁵

In a prospective study of 76 consecutive infertile women in sub-Saharan Africa, Ahmadu Bello University Teaching Hospital, Shika-Zaria Kaduna State, Nigeria, Over a period of 40 months, on treatment outcome of hyperprolactinemic infertility, 40.8% (31 patients) presented with primary infertility and 59.2% (45 patients) with secondary infertility. The commonest menstrual disorder was oligomenorrhoea occurring in 39 (51.3%) patients; this was followed by secondary amenorrhoea in thirteen (17.1%) patients. Normal menstrual cycle and flow was recorded in 24 (31.6%) patients. Of the 76 patients, 63 (82.9%) had galactorrhoea and 57 (75%) were found to have anovulatory cycles.⁶

In a prospective analysis of 30 women on natural history of untreated hyperprolactinoma at the University of Iowa between 1979 and 1983, 18 women had amenorrhea (primary in 2), 8 had oligomenorrhea, and 4 had regular menstrual periods, Nineteen women had galactorrhea.¹⁴

In a retrospective study done at Tikur Anbessa Specialized Hospital (TASH) National Endocrinology Referral Clinics, Addis Ababa (AA), and Ethiopia, to assess the magnitude,

clinical presentation and outcome of pituitary lesions, Out of the 1124 patients seen at national endocrine referral clinics of TASH during the study period, 51 (4.54%) patients were diagnosed to have pituitary lesions. Nine patients were excluded from analysis because of inadequate information on the chart. A total of 42 patients with confirmed pituitary lesions were included in the analysis out of which 30 (71.4%) were females and 12 (28.6%) males. the age range was from 14 to 60 years. Old (median age was 29.5 years and mean age was 32.5 years. Twenty (47.6%) had prolactinoma, 9 (21.43%) Cushing disease, 7(16.67%) acromegaly, 2 (4.76%) patients had features of both prolactinoma and acromegaly, 2 (4.76%) presented with panhypopituitarism, 1 (2.38%) presented with hypogonadism and 1 (2.38%) had nonfunctioning pituitary adenoma (Table 2). the mostcommon presenting symptoms were headache and visual disturbances in 33(78.6%) and 20(47.6%) of patients respectively.¹¹

Diagnosis of prolactinoma

Prolactinoma diagnosis is based on clinical, laboratory and imaging characteristics. Most women harbor microprolactinomas in which symptomatology is related to hypogonadism and galactorrhea. Patients with macroprolactinomas often present, in addition, mass effects symptoms, as headache, visual disturbances and additional hypopituitarism.¹⁵

According Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas revised on 2006, serum prolactin levels parallel tumour size. PRL values between the upper limits of normal and 100 µg/l (~2000 mIU/l) may be due to psychoactive drugs, oestrogen, or functional (idiopathic) causes, but can also be caused by microprolactinomas. Most patients with PRL levels over 150 µg/l (~3000 mIU/l) (five times higher than the normal values) will have a prolactinoma. Macroadenomas are typically associated with levels of over 250 µg/l (~5000mIU/l), and in some cases over 1000 µg/l (~20000 mIU/l). Nevertheless such values are not absolute; prolactinomas can present with variable elevations in PRL, and there may be dissociation between tumour mass and hormonal secretion. Therefore, caution must be exercised when interpreting a moderate elevation of PRL in a patient with a pituitary macroadenoma, because the cause of the hyperprolactinaemia may be compression of the pituitary stalk by a tumour other than a prolactinoma.¹⁶

In an online survey of a large sample of physicians from middle and North Africa 468 respondents were included; 36 % were endocrinologists; 49 % worked in public facilities and 81 % graduated more than 10 years. 40 and 30 % would have seen 1–5 and more than 5 suspected or confirmed prolactinomas over a 6 months period, respectively .Regarding the diagnosis, 30 % of the respondents considered that prolactin levels <100 ng/ml exclude the presence of a prolactinoma. 21 % of respondents considered prolactin levels >250 ng/ml compatible with macroprolactinomas only, whereas others accepted this to be compatible also with microprolactinomas, macroprolactinaemia and drug-induced hyperprolactinemia (50, 42 and 36 % respectively). 71 % of respondents favored the screening for macroprolactin in asymptomatic individuals with hyperprolactinemia.⁹

Treatment response of patients with prolactinoma

Dopamine agonists are currently the primary treatment for patients with prolactinomas. For over 20 yr, bromocriptine has been used as the dopamine agonist of choice in that it was proven effective in decreasing both the size of pituitary adenoma and serum prolactin (PRL).¹⁷

In a case series in Cameroonian population all patients were treated with Cabergoline and one non-secreting macroadenoma with visual signs required additional surgical treatment. The duration of follow up was 8-16 months. After three months of treatment, 8 of 10 patients with amenorrhea had menses, 12/18 had no more galactorrhea. Prolactin levels normalized in 16/25. Fertility was restored with confirmed pregnancy in 7/17 by the 16th month of follow up. Serum prolactin levels decreased significantly at month 2-3 ($p = 0.025$).⁵

Based on contemporary literature and article review normoprolactinemia is obtained in 71–100% of patients with microprolactinomas by TSS. Almost equal results are found in circumscribed intrasellar macroprolactinomas. In experienced hands, pituitary function is preserved in TSS. They found early remission in 78.1% of intrasellar prolactinomas (including microprolactinomas), in 59.4% of suprasellar prolactinomas without visual deficits, in 13.5% of suprasellar prolactinomas with visual deficits, in 24.3% of parasellar and/or sphenoidal prolactinomas, and in 0% of giant prolactinomas. The risk of cardiac valve disease is still a concern with ergot-derived dopamine-agonists (DAs) in patients requiring long-term, high-dose dopamine-agonist (DA) treatment. Cost-utility analysis favors TSS over DA treatment.¹⁸

In a prospective study of 76 consecutive infertile women with hyperprolactinemia over a period of 20 weeks in sub-Saharan Africa, Ahmadu Bello University Teaching Hospital, Shika-Zaria Kaduna State, Nigeria, two dosage regimen were used based on the pretreatment prolactin level; less than 50ng/ml had 0.25mg twice weekly ($n=58$) and 50ng/ml and above 0.5mg twice weekly ($n=18$), normalization of prolactin level was achieved in 75 (98.7%) patients. At the end of the study period, there was resumption of menstrual flow in 10 (76.9%) of the 13 patients that were amenorrhoeic and all the 39 (100%) patients that were oligomenorrhoeic had their normal menstrual cycle restored. Resumption of ovulatory cycles occurred in 87.7% of those with anovulatory cycles. Of the 76 patients, 69 (90.8%) got pregnant during the 20 weeks study. However, out of the 69 that got pregnant, 13 (18.8%) got pregnant while on cabergoline therapy. There was no case of cabergoline resistance or discontinuation recorded in this study.⁶

OBJECTIVE

General objective – To assess the clinical characteristic, diagnosis and treatment response of adult patients with prolactinoma on follow up at endocrine clinic of TASH

Specific objective

To identify the clinical characteristic of patients with prolactinoma

To determine the laboratory profile and imaging characteristics of patients with prolactinoma

To assess the treatment response of patients with prolactinoma

To assess the association of tumor size with prolactin level and clinical manifestation

Methods and materials

Study area

The study was conducted at TikurAnbessa specialized hospital, one of the oldest and major hospital in the country.

TikurAnbessa Specialized Hospital is the largest referral hospital in the country since 1972. It was transferred to School of Medicine in 1998 by the Federal Ministry of Health, and it has since become a University teaching hospital. TASH is now the main teaching hospital for both clinical and preclinical training of most disciplines. It is also an institution where specialized clinical services that are not available in other public or private institutions are rendered to the whole nation.

Endocrine unit is one of the big units in the compound participating in both academic and clinical activities with a national endocrine referral clinic running 4 days per week. An average of 18,500 patients are seen annually with an average of 80 patients per clinic with a variety of Endocrinologic cases and diabetes. Diabetes comprises the majority of cases seen at clinics. Friday is the regular visit day for most of patients with prolactinoma though there are patients with prolactinoma seen on other days.

Source population

The source population is all patients seen at endocrine clinic of TASH during the study period

Study population

Patients with confirmed prolactinoma on follow up at Endocrine clinic of TASH

Study design

A hospital based retrospective cross sectional study was conducted on adult patients with confirmed prolactinoma attending TikurAnbessa Specialized Hospital, national Endocrine referral clinic.

Sample size determination

All patients on follow up for prolactinoma at endocrine clinic for 5 years, from June 2007 E.C to June 2012 E.C fulfilling the inclusion criteria were included.

Data collection

Data was collected from the charts and electronic medical records of patients with prolactinoma on follow up at endocrine clinic from June 2015 to June 2020 using a structured questionnaire prepared in English. The medical record number of patients was retrieved from endocrine registry log book. The study variables were included on the questionnaire. Data was collected by the principal investigator.

Data quality control

After questionnaire development it was pretested on 5% of sample and modification on the questionnaire was done accordingly. Data quality was checked on daily basis for completeness, clarity and accuracy before data entry.

Data analysis and presentation

Before analysis each collected data was verified, validated and recorded. The IBM SPSS statistic software package version 26 was used for entry and analysis of data.

Descriptive statistics was used as a statistical data analysis method and presented as frequencies and percentages with their corresponding confidence intervals. To help in better communication of results simple frequencies and percentages are organized in tables. Continuous variables are represented as means, standard deviations and minimum and maximum values and categorical variables as frequencies. Logistic regression analysis is used to assess associations. Confidence interval of 95% is estimated for all variables and p-value < 0.05 is considered to indicate statistical significance.

Inclusion and exclusion criteria

Inclusion criteria

- Patients with confirmed prolactinoma on follow up and treatment at least for 2 months
- age > 14 years

Exclusion criteria

- Patients with incomplete records (lost charts or charts with incomplete records of the necessary variables of the study)

-pregnant and/or lactating mother with galactorhea, but no imaging evidence of pituitary adenoma.

Study variables

Dependent variable

-clinical features of the study subjects (amenorrhea, galactorhea, loss of libido, visual disturbance, headache, infertility)

-Biochemical profiles – serum prolactin level

-treatment response

Independent variable

- Sociodemographic factors- age, sex, marital status, place of residence

-MRI finding

-duration of treatment and follow up

Operational definition

Prolactinoma- elevated serum prolactin level with imaging evidence of pituitary adenoma.

Recent prolactin level- serum prolactin level determined within the last 3 months.

Ethical consideration

Before conducting the study, the study proposal was submitted for approval to department of internal medicine and ethical clearance was issued by ethical review committees of the department. As the study was conducted from chart review, data was collected anonymously and kept confidential. No personal identifications were used on the data collection tool. The collected data was accessed only by the investigator and confidentiality was kept at all levels of the study.

Dissemination of results

The results of the study will be presented to department of internal medicine, college of health sciences and to all stakeholders working on issues related to infertility and endocrinology. Finally the manuscript will be sent for publication to local and international scientific journals in related fields.

Result

Out of the 217 patients with pituitary adenoma seen at the national endocrine referral clinic during the study period 91(41.9%) patients were diagnosed to have prolactinoma. 22 patients were excluded from the analysis because of incomplete information on their chart (fig.1).A total of 69 patients with confirmed prolactinoma were included in the analysis out of which 53 (76.8%) were females and 16 (23.2%) were males. The age range was from 19 to 52 years Old with a mean age of 30.78 years ($SD\pm 7.97$). Most of the patients (41/ 69, 59.4%) are from Addis Ababa (table 1).

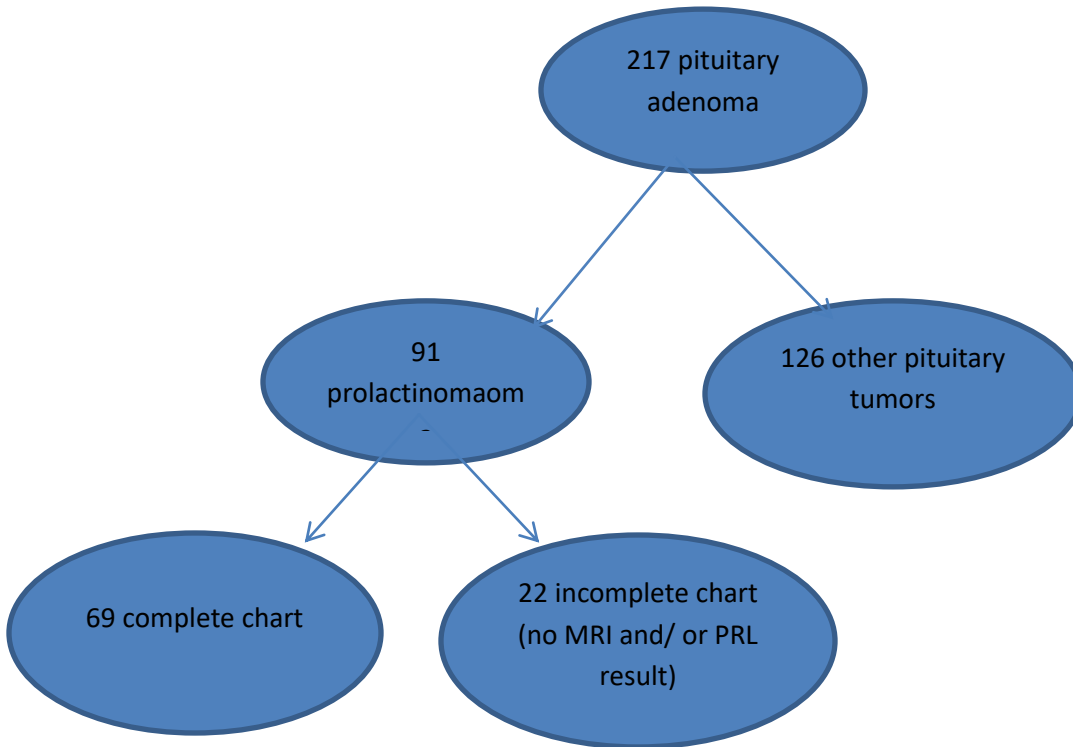


Fig.1-Flow chart of patients with prolactinoma at National Endocrine Referral clinics, TASH, June 2015 to June 2020.

Table 1: Sociodemographic characteristics of patients with prolactinoma at National Endocrine Referral clinics, TASH, June 2015 to June 2020.

Age	Minimum	Maximum	Mean	SD
	19	52	30.78	7.974

Variable	Category	Frequency	Percentage
Sex (n=69)	Male	16	23.2
	Female	53	76.8
Region (n=69)	Addis Ababa	41	59.4
	Oromia	15	21.7
	Amhara	5	7.2
	SNNPR	8	11.6

Headache was the major presenting symptom occurring in 47(68.1%) patients followed by visual disturbance seen in 34(49.3) patients. Among the 53 female patients 30(56.6%) had amenorrhea, 16 (30.18%) had galactorrhea, 10 (18.86%) had infertility, 2 (3.77%) had unexplained weight gain, 4 (7.54%) had menstrual irregularity and 2 (3.77%) had bone pain. Male patients presented with either headache or visual disturbance. (table2).

All patients with prolactinoma had high serum prolactin level at diagnosis with the minimum prolactin level of 30 ng/ml, maximum level of 6705ng/ml, and mean prolactin level of 829.74ng/ml with SD±1281.99(normal range 2.5-25 ng/ml).All patients had pituitary MRI at diagnosis. 55 out of the total sixty nine (79.7%) patients had macroadenoma (tumor size >10mm in any of the dimensions) while 14(20.3%) patients had microadenoma(tumor size <10mm in any of the dimention). All of the Male patients had macroadenoma(table 2).

12 out of the total 69 patients had additional endocrine disorders, 3(25%) acromegaly, 5(41.7%) hypothyroidism, 1(8.3%) gonadal disorder and 3(25%) panhypopituitarism. Comorbidities like diabetes, hypertension, HIV were seen in 8 patients out of the 69 patients (3, 2, 2, and 1 patient respectively).

Table 2: Clinical, laboratory and MRI features of patients with prolactinoma at National Endocrine Referral clinics, TASH, June 2015 to June 2020.

Variable	Category	Frequency (percentage)			
		Female (n=53)		Male (n=16)	
		Yes	No	Yes	No
Presenting symptom	Amenorrhea	30(56.6%)	23(43.4%)	NA	
	Headache	34(64.1%)	19(35.9%)	13(81.25%)	3(18.75%)
	Visual disturbance	21(39.62%)	32(60.38%)	13(81.25%)	3(18.75%)
	Infertility	10(18.86%)	43(81.14%)	0	16(100%)
	Galactorrhea	16(30.18%)	37(69.82%)	0	16(100%)
	Unexplained Weight gain	2(3.77%)	51(96.23%)	0	16(100%)
	Menstrual irregularity	4(7.54%)	49(92.46%)	NA	
	Bone pain	2(3.77%)	51(96.23%)	0	16(100%)
Initial PRL level	<250 ng/ml	29(54.71%)	24(45.29%)	2(12.5%)	14(87.5%)
	250-500 ng/ml	14(26.41%)	39(73.59%)	5(31.25%)	11(68.75%)
	>500 ng/ml	10(18.86%)	43(81.14%)	9(56.25%)	7(43.75%)
MRI feature	Macroadenoma	39(73.58%)	14(26.42%)	16(100%)	0
	Microadenoma	14(26.41%)	39(73.59%)	0	16(100%)

NA=not applicable

Treatment was started for 67 out of the 69 patients. 56 patients (81.2%) were treated with medical therapy alone, 9(13%) patients were treated with both medical and surgical therapy and 2 patients undergo surgery without medical therapy. 2 out of the sixty nine patients had only follow up without treatment. Among the patients treated with medical therapy 61 (93.8%) patients took bromocriptine and 4(6.2%) patients took cabergoline. The duration of treatment was variable with a mean duration of follow up of 3.25 years (3 months-15 years). Out of the eleven patients who underwent surgery, the indication for surgery was tumor mass effect in 6/11 patients and failed medical therapy in 5/11 patients.

From the total 69 patients 59 patients (85.5%) had clinical response and ten (14.5%) had no clinical response. The clinical responses include improvement in headache (38/47), improved visual disturbance (23/34), no more galactorrhea (12/16), regular menstrual flow (13/30) and restoration of fertility with confirmed pregnancy (6/10).out of the six patients who get pregnant during their follow up one had worsening and five had improvement of their clinical symptom during their course of pregnancy. The outcome of the pregnancy was alive baby in 5 of the 6 pregnant mothers and 1 patient is pregnant on follow up.(fig.2)

Only 50 patients had recent prolactin level and 44 out of 50 patients had Serum prolactin decreased, 5 out of 50 patients had their prolactin level increased and 1 out of 50 patients had same prolactin level to the initial prolactin level.

The response with regard to the tumor size was assessed only in 30 out of 69 patients because these are the only patients who had a repeat MRI done after initiation of treatment. Tumor size shrinkage was seen in 17 out 30 patients, tumor size increased in 2 out of 30 patients, 5 out of the 30 patients had no change in their tumor size and 6 out of the 30 patients had empty sella on their repeat imaging.

Treatment was discontinued in 16 out of the 65 patients. Disease remission was the major reason for treatment discontinuation (10 out of 16 patients) followed by financial reason (5 out of 16 patients) and drug side effect (1 out of 16 patients). The drug side effect was easy fatigability.

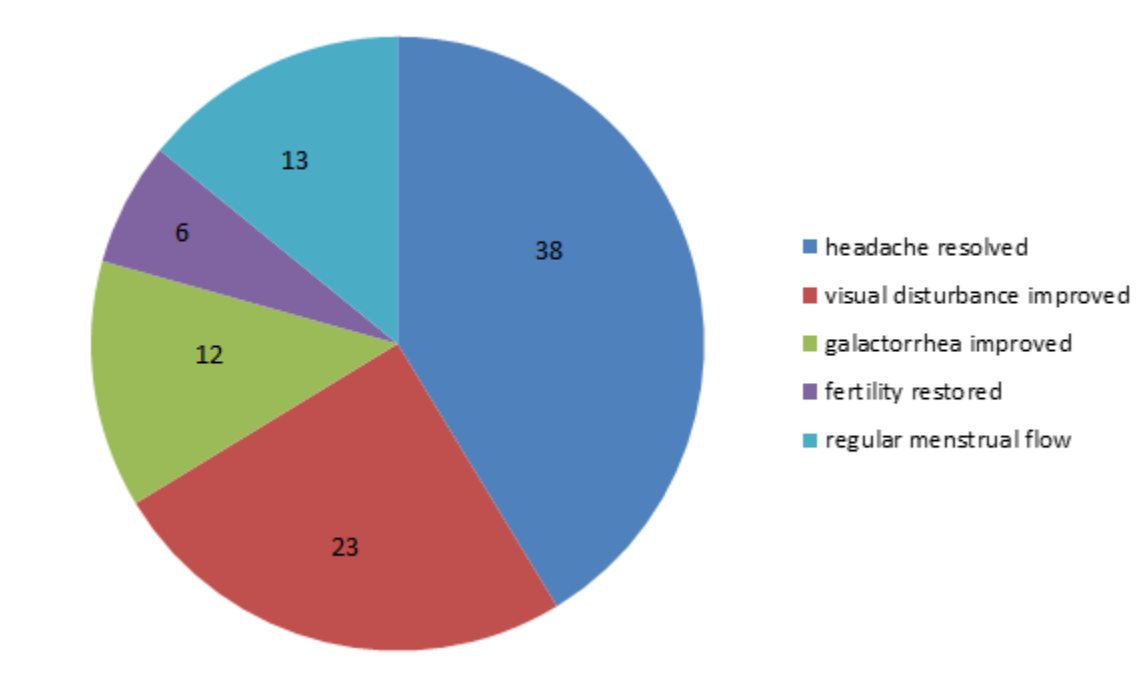


Fig 2. Treatment response of patients with prolactinoma at National Endocrine Referral clinics, TASH, June 2015 to June 2020.

Out of 67 patients who received treatment and out of the 30 patients who had repeat imaging only 17 (25.4%) patients had a decrement in their tumor size while none of the patients from those who haven't started treatment has repeat MRI which makes it difficult to draw conclusion on the response of the tumor size without treatment.

Table 3-cross tab of treatment with change in size of tumor, in patients with prolactinoma at National Endocrine Referral clinics, TASH, June 2015 to June 2020.

			change in tumor size					Total
			Decrease d	increase d	sam e	empt y sella	NA	
treatment started	Yes	Count	17	2	5	6	37	67
		% within treatment started	25.4%	3.0%	7.5 %	9.0%	55.2%	100.0 %
	No	Count	0	0	0	0	2	2
		% within treatment started	0.0%	0.0%	0.0 %	0.0%	100.0 %	100.0 %
Total		Count	17	2	5	6	39	69
		% within treatment started	24.6%	2.9%	7.2 %	8.7%	56.5%	100.0 %

On bivariate logistic regression the initial size of the tumor is associated with the presenting clinical symptom (headache, visual disturbance, infertility). Patients with macroadenoma are more likely to develop headache than patients with microadenoma with p value <0.029, and COR of 3.9, 95% CI (1.2, 13.2). Macroadenomas are also associated with development of visual disturbance than patients with microadenomawith p value <0.009, and COR of 8.35, 95% CI (1.7, 40.9), but they are less likely to present with infertility at initial presentation than patients with microadenoma with p value <0.019, COR of 0.18, 95%CI (0.043, 0.751). Patients with macroadenoma had PRL levels >250ng/ml and those with microadenoma had PRL levels<=250ng/ml with p value<0.003, COR of 11.368, 95%CI (2.303, 56.128). But on multivariate logistic regression only the prolactin level has strong association with the initial tumor size with p value <0.003, AOR of 19.51, 95% CI (2.689, 141.6).

Table 4 : Variables found to have significant association on bivariate logistic regression

	P value	COR	95% CI for COR	
			Lower	Upper
Initial tumor size with headache	0.029	3.905	1.153	13.227
Initial tumor size with visual disturbance	0.009	8.348	1.702	40.933
Initial tumor size with infertility	0.019	0.180	0.043	0.751
Initial tumor size with prolactin level	0.003	11.368	2.303	56.128

Table 5-variable found to have significant association on multivariate logistic regression

	P value	AOR	95% CI for AOR	
			Lower	Upper
Prolactin level with initial tumor size	0.003	19.512	2.689	141.604
Headache with initial tumor size	0.060	5.851	0.925	37.009
Visual disturbance with initial tumor size	0.142	3.942	0.632	24.585
Infertility with initial tumor size	0.232	0.322	0.050	2.067

Discussion

In this study prolactinomas accounted for 41.9% of the pituitary tumors which is comparable to similar studies which has shown that pituitary tumors appear to occur in 10-15% of the general population out of which prolactinomas are the most common pituitary adenomas accounting for upto 45% of pituitary tumors.^{16,19,20}. An earlier study from Ethiopia on magnitude, clinical presentation and outcome of Patients with Pituitary Lesions had similar findings that prolactinomas accounted for 47.9% of the pituitary lesions¹¹. In another CrossSectional Study in the Province of Lie`ge, Belgium, prolactinomas were the most frequent tumor found (45 of 68; 66.2%).²¹

Most (76.8%) of the patients in this study were females and the mean age was 30.78 years, which is similar to other studies^{5,11,22}. Headache (68.1%) and visual disturbance(49.3%) were the two most common presenting symptoms as most (79.9%) of the patients had macroadenoma, which is consistent with the other study done in Ethiopia on pituitary lesions and opposite to the findings in guidelines of the Pituitary Society for the diagnosis and management of prolactinomas and other similar studies from Churchill Hospital, University of Oxford and University of Douala, Douala, Cameroon where the main presenting feature is infertility and microadenoma is the common finding^{11,16,22,23,5}. The possible reasons for this disparity could be the difference in health care seeking behavior of the society and the availability of diagnostic modalities like MRI. In developed world there is the behavior of early medical seeking that will result in early identification of smaller lesions unlike the situation in the developing world where patients come late and at times also imaging are done late after the tumors are grown. Besides, the treatments for prolactinomas are not readily and easily available for most parts that will impact the tumor sizes to be larger in our patients' population.

Regarding the diagnosis, all patients with prolactinoma in this study had serum prolactin level measured and MRI of the pituitary at diagnosis as per the recommendation of Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas and endocrine society practice guideline^{7,16} and similar to other studies from different countries^{3,22}. Most of the female patients(54.71%) present with an initial PRL level <250ng/ml whereas most of the male patients(56.25%) had an initial PRL >500ng/ml and all of our male participants(100%) had macroadenoma which strengthens the finding of an association between tumor size and the PRL level, and is consistent with findings from Brussels, Belgium.²³

This study has showed an association of tumor size to the prolactin level and clinical symptoms which is consistent with findings from other similar studies.^{7,22}

In this study 56(81.2%) patients were treated with medical therapy alone and 9(13%) patients were treated with combination of medical and surgical therapy. out of the 65 patients treated medically 61(93.8%) patients took bromocriptine and only 4(6.2 %) patients took cabergoline. This is consistent with the endocrine society clinical practice guideline recommendation to start dopamine agonists to lower prolactin levels, decrease tumor size, and restore gonadal function

for patients harboring symptomatic prolactin-secreting microadenomas or macroadenomas , but the first line dopamine agonist of choice is cabergoline⁷.Most of our study participants were on bromocriptine mostly because of inavailability of cabergoline and in part because most of them are in childbearing age and planning to conceive.

Treatment was discontinued in 16(24.61) patients, disease remission being the leading cause for discontinuation followed by financial reason.

Limitation of the study

Due to the COVID-19 pandemic Patient flow has decreased significantly and follow up clinics are partially made virtual which might affect the quality of data.

This is a single centered hospital based retrospective chart review which makes it difficult to generalize the results.

The limited number of participants and incomplete data in some charts might affect the result

Strength of the study

One strength of this study is that the data is collected by the principal investigator where data quality is seriously followed.

The other strength is its long duration (5 years).

Conclusion

Prolactinomas are the most common secretory pituitary tumors accounting for 41.9% of the pituitary adenomas. The initial tumor size has association with the presenting symptom and initial prolactin level. Unlike the findings from other similar studies most patients in this study had macroprolactinoma and this could be due to delayed medical seeking behavior. The initial tumor size was associated with serum prolactin level with p value <0.003, AOR of 19.51, 95% CI (2.689, 141.6).Patients with prolactinoma had good clinical response to medical therapy alone.

Recommendation

This study showed Prolactinomas are the commonest pituitary tumors with the findings of macroprolactinomas as the commonest finding. This entails that facilities to diagnose prolactinoma including serum prolactin levels and pituitary imaging with either CT-scan or MRI should be made available for early diagnosis and treatment.

Dopamine agonists should be made available in public health facilities as financial limitation is one of the causes for treatment discontinuation.

Further prospective studies are recommended in the future to assess the diagnosis and treatment response of the prolactinoma.

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Annex

Questionnaire

Card number of the patient----- Icare ID----- Code -----

I-Sociodemographic data

1- Age-----

2-Sex A-Male B-Female

3-Region----

4-Ethnic background-----

II-Clinical presentation

-presenting symptom

1 –amenorrhea A-yes B-no

2- Galactorrhea A-yes B-no

3- Erectile dysfunction A-yes B-no

4- Infertility A-yes B-no

5-Headache A-yes B-no

6-visual disturbance A-yes B-no

7-Bone pain A-yes B-no

8-Other symptom, specify-----

III-Diagnosis

1-initial prolactin level A-yes B-no

2-if yes----- ng/mL

3- Recent prolactin level A-yes B-no

4-if yes-----ng/mL

5-brain imaging at diagnosis A-yes B- no

6- If yes, initial tumor size -----

7- Repeat imaging A=yes B=no

8- If yes, tumor size-----

IV-Treatment

1- Treatment started A=yes B= no

2-if yes, type of treatment A-medical B-surgical

3-if medical, w/c drug A-Bromocriptine B-cabergoline

4-duration of treatment-----

5-did the patient responded clinically? A=yes B=no

6-If yes for the above question, what is the clinical response?

6.1-conception achieved (pregnancy) A=yes B=no

6.2- headache has resolved A- yes B=no

6.3-galacorrhea has resolved A=yes B=no

6.4-visual disturbance has improved A=yes B=no

7-if the answer for the above question is pregnancy achieved, how is the profile during pregnancy?

A-symptoms resolved

B-prolactin level dropped from the initial value

C-tumor size regressed

d- Prolactin level same or increased

8- Medical treatment discontinued A=yes B= no

9- If yes, reason for discontinuation

9.1-Financial reason A=yes B=no

9.2-Remission A=yes B=no

9.3-Drug side effect A=yes B=no

10-If treatment discontinued for drug side effect, specify

V-additional information

1- Comorbidities A=yes B=no

2-If yes

2.1-Diabetes A=yes B=no

2.2-renal failure A=yes B=no

2.3- Obesity A=yes B=no

2.4- Others, specify-----

3-additional endocrine problem A=yes B=no

4- If yes, which one

4.1-Acromegally A=yes B=no

4.2-Hyperthyroidism A=yes B=no

4.3-gonadal disorder A=yes B=yes

5-for patient on medical treatment for >2 years, was there screening for valve fibrosis?

A=yes B=no

6-what was the reason for referral and what was done at referring center?

A- Sent without any investigation and management

B- Sent with elevated prolactin level only, treatment not started

C- Sent with elevated prolactin level and imaging results, treatment not started

D- Started on treatment with laboratory evidence only and no response

E- Started on treatment with laboratory and imaging evidences but no response