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ORIGINAL RESEARCH

Immunohistochemical and Clinicopathologic Profiling of Pituitary Adenomas at a Nigerian Tertiary Hospital

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Abstract

Background: Pituitary adenoma is the most common pituitary tumour and the third most common intracranial tumour worldwide. Only a few studies have been done in Africa on the immunohistochemical expression pattern and clinicopathologic presentations of the different hormonal subtypes of pituitary adenomas.

Objective: To evaluate the immunohistochemical hormonal profiles and clinicopathologic behaviour of pituitary adenomas diagnosed within ten years at the Lagos University Teaching Hospital, Lagos, Nigeria.

Methods: In this 10-year retrospective, cross-sectional study, all cases of pituitary adenomas diagnosed at the hospital mentioned above between 1 January 2009 and 31 December 2018 were analysed. Their paraffin-embedded tissue blocks were stained with haematoxylin and eosin and then with immunostains for growth hormome (GH), adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH), follicular stimulating hormone (FSH), luteinizing hormone (LH), and prolactin (PRL), using their standard immunohistochemistry protocols.

Results: Seventy pituitary adenoma cases were studied. The male-to-female ratio of the patients was 1.6:1. The median age was 45 years, and the peak age of occurrence was the fifth decade for both sexes. Most were null cell adenomas (44.7%) and FSH-beta gonadotrophs (22.9%). The least diagnosed were thyrotroph (1.4%) and corticotroph adenomas (1.4%). Most of the adenomas were macroadenomas, and the most common presenting symptom was visual impairment.

Conclusion: Pituitary adenoma is commoner in males in their 5th decade of life at the Lagos University Teaching Hospital, Lagos, Nigeria. The null cell adenoma is the commonest type of pituitary adenoma diagnosed in the center, and the majority of the patient diagnosed with pituitary adenoma present late with complications of visual impairment.

Keywords: Adenoma, Clinicopathologic, Immunohistochemistry, Pituitary, Tumour, Visual impairment.

Introduction

Pituitary adenomas are the third most common intracranial neoplasm worldwide. [1] However, there are variations in the frequency of pituitary adenomas from reports of various institution-based studies in Nigeria, with many ranking it as the third most common intracranial tumour. In contrast, some ranked it as the second most common or the most common intracranial tumour in their studies. [2-13] Pituitary adenoma accounts for 15% of all primary intracranial tumours in adults. [14] Its prevalence in the Western world is 5%-20% in cancer registry figures, 14% in autopsy data and 22.5% in radiology studies. Its prevalence in Nigeria ranges between 16.8% and 22.5%. [15, 16]

The pituitary gland is a small bean-sized, ovoid organ located in the midline, at the base of the brain, in a bony pouch called the sella turcica. [17] It is composed of larger anterior and smaller posterior lobes. It produces and releases growth hormones (GH), adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH), follicular stimulating hormone (FSH), luteinizing hormone (LH), and prolactin (PRL). [17] These hormones regulate the secretion of other hormones from other organs in the body. [17] Histologically, using Haematoxylin and Eosin (H&E) stain, the cells of the anterior pituitary gland consist of 50% chromophobes (non-secretory), 35% acidophils (which secrete GH and PL), and 15% basophils (which secrete ACTH, TSH, FSH, and LH). [18,19]

A pituitary adenoma is a neoplastic proliferation of the hormone-producing cells of the anterior pituitary. They are usually benign but can invade adjacent structures. [14] According to their sizes, they can be microadenomas (< 1.0 cm in diameter), macroadenomas (1.0 to 4.0cm in diameter), or giant adenomas (> 4cm in diameter). [14] Macroadenomas and giant adenomas can compress or invade adjacent structures, including the optic chiasma and cavernous sinus. [14] Adenomas are termed functional when they produce excess hormones with symptom manifestation.[14] They are termed silent (non-functional) when there are no clinical signs or serum hormonal elevation. The hormone produced by these silent tumours can be demonstrated using immunohistochemistry. [14]

Pituitary adenomas have two broad presenting features, including their endocrine disturbances with features of either hypopituitarism or hyperpituitarism and relationships to adjacent structures. [14,19,20] Optic chiasma compression causes bitemporal hemianopia and diplopia. [14,19,20] Larger tumours may involve the hypothalamus, causing diabetes insipidus and obesity. [19,20]

The morphological classification of pituitary adenoma into basophils, acidophils, and chromophobes adenomas using their Haematoxylin and Eosin (H&E) staining characteristics is limited by its inability to elucidate the hormonal phenotypes of the tumour. In 2004, the WHO classified pituitary tumours into three subcategories - typical pituitary adenoma, atypical pituitary adenoma, and carcinoma. [21] Atypical pituitary adenomas have a high Ki-67 proliferative index (>3%), high mitotic activity, and strong nuclear p53 staining. [21] The typical adenomas were classified based on their various hormonal immunohistochemical reactivities. [21]

In 2017, the fourth edition of the WHO Classification of Tumours of Endocrine Organs discarded the term "atypical pituitary adenoma" due to its poor prognostic significance.[14] Some of the criteria for defining atypical pituitary adenoma, such as high mitotic rates and Ki-67 labelling indices, were used by the WHO to define aggressive pituitary adenoma.[14] Pituitary

adenomas were classified based on their cell lineage and routine immunohistochemistry for transcription factors that regulate anterior pituitary hormones (GH, PRL, TSH-beta, ACTH, FSH-beta, LH-beta, and alpha subunits) and those that regulate cell differentiation such as PIT-1, SF-1, and T-PIT. [14] The fourth edition of the WHO Classification of Tumours of the Endocrine Organs utilizes hormonal profiling using immunohistochemistry as the gold standard for diagnosing pituitary adenoma.[14] Hormonal immunohistochemistry can be used to classify them into seven main subtypes: corticotrophs (ACTH), somatotrophs (GH), lactotrophs (prolactin), thyrotrophs (TSH), gonadotrophs (FSH± LH), null (immunonegative and transcription factor negative), and plurihormonal. [14] Pituitary carcinoma is rare and is only diagnosed when metastases are present.[14]

Pituitary neuroendocrine tumour (PitNET)" has replaced the term "pituitary adenoma" in the 2022 WHO Classification of Endocrine and Neuroendocrine Tumours with the provision of the tumour subtype information. [22,23] Pituitary carcinoma was replaced with the term "metastatic PitNET". This new WHO classification emphasizes the accurate classification of PitNET/PA by histologic typing and subtyping based on immunohistochemistry for lineage-restricted pituitary transcription factors. [22,23] Transcription factor negative immunohistochemical staining indicates PitNET/PA with no identified cell lineage, including the null cell and plurihormonal adenomas. [22,23]

This approach to the classification of PitNET/PA, however, does not fully elucidate the complexity of pituitary tumorigenesis.[23] This shortcoming of the new approach has limited its application in clinical practice. The prognostic relevance of this new classification has yet to be fully validated. [23] Furthermore, this new system can only be used

for follow-up plans and adjunctive treatment after surgery. It has no application in treatment strategies. [23] A more clinically relevant, standardized, integrated approach incorporating morphology and molecular techniques has been recommended. [22]

Resource-poor countries like Nigeria utilize tumour morphology and immunohistochemical hormonal profiling to classify PitNETs/PAs, as this provides the essential information for accurate diagnosis and optimal management. Only a few studies have been done to evaluate the immunohistochemical hormonal profile and clinical behaviour of pituitary adenomas in Nigeria. [24, 25] Identifying the hormonal immunophenotypes and their clinicopathologic evaluation is essential in managing PitNETs/PAs in resource-poor countries.

This study aimed to determine the demographic distribution, clinicopathologic presentations, and hormonal immunohistochemical profiles of all pituitary adenomas diagnosed histologically at the Lagos University Teaching Hospital Lagos (LUTH), Nigeria, between the 1st of January 2009 and 31st of December 2018. The study also highlighted the clinical presentations of these pituitary adenomas.

Methods

The study was a ten-year hospital-based, retrospective study. Samples included in this study were all the histologically diagnosed pituitary adenoma cases obtained from surgical resections in the Department of Anatomic and Molecular Pathology, LUTH, within the study period. Important clinical information was retrieved from patients' hospital records and histopathology results. The clinical presentations and tumour sizes of the various

immunophenotypes of pituitary adenomas were recorded.

Ethical considerations

The study was approved by the Health Research and Ethics Committee of Lagos University Teaching Hospital (LUTH), with the assigned number ADM/DSCST/HRC/APP/5792. Patients' confidentiality was protected by non-disclosure of their personal identities and encryption of their hospital and laboratory numbers.

Procedures

Paraffin-embedded tissue blocks and their corresponding routine H&E-stained slides of pituitary adenomas were retrieved. Only 70 out of the 88 pituitary adenoma cases diagnosed within the study period were included. Most of the formalin-fixed paraffin-embedded (FFPE) tissue blocks of pituitary adenoma cases diagnosed between the 1st of January 2009 and the 31st of December 2010 were either missing or damaged and, as such, were excluded from the study. New sections of these paraffin-embedded tissue blocks of the included pituitary adenoma cases were made and re-stained with H&E and reticulin. All slides were then reviewed and confirmed histologically as pituitary adenoma.

Biopsies for tissue microarray (TMA) were taken by making 2mm circular punches on the paraffin-embedded tissue blocks of these cases. The TMAs were sectioned and stained with ACTH (Dako, x 500 dilution, condition: /16¹), GH ((Dako, x 4000 dilution, condition: /16¹), LH (Dako, x 400 dilution, condition: /16¹), FSH (Dako, x 200 dilution, condition: 32/16), TSH, (Dako, ready-to-use, condition: 24/16), PRL (Ventana, x 200 dilution, condition: x 1/2¹) immunostains using their standard protocols to identify the subtypes of pituitary adenoma. Maximal antigen retrieval was ensured using thin slices of deeper sections, lengthened heat antigen retrieval method with EDTA buffers (pH8) and charged slides. Normal anterior pituitary tissues harvested at autopsy were used as positive controls.

Data analysis

The demographic and clinical data were summarized using standard descriptive statistics mean, median ± standard deviation [SD]) and frequency tabulation (%). The Statistical Package for Social Sciences version 27 (New York: IBM Inc) was used to analyse the data.

Results

Within the study period, pituitary adenomas accounted for 28.7% of all primary intracranial tumours diagnosed in LUTH following surgical biopsy (Table I).

Of the 88 pituitary adenoma cases, 70 met this study's inclusion criteria. Most of the patients were males (43; 61.4%). The male-to-female ratio was 1.6:1 (Table II). The median age of the 70 patients with pituitary adenoma was 45 years (interquartile range: 20.75) (Table II). Their age range was 15 years to 69 years (Table II). The median age of the males was 47 years (interquartile range: 18) and 43 years (interquartile range: 24.5) for the females (Table II). The fifth decade of life (41 to 50 years) was the peak age of occurrence for both sexes, constituting 35.71% of all pituitary adenoma cases (Figure 1). Histologically, using H&E stain, most (30, 43%) of the adenomas were basophilic. Twenty-three (33%) of the adenomas were chromophobic, while 17 (24%) were acidophilic. The photomicrographs of each of the histologic types of adenomas seen in the study are shown in Figure 2. Null cell adenomas were the most common subtype (Figure 3), occurring in 32 (45.7%) with a mean age of 48.81±11.06 years (Tables II and III). This subtype had a male-to-female ratio of 1.9:1 (Table II). They were also seen primarily in patients in their fifth decade of life (Table IV).

Table I: Distribution of histologically diagnosed primary intracranial tumours at the Lagos University Teaching Hospital (LUTH)

Primary Intracranial Tumours	Frequency	Proportions
Meningioma	113	36.8
Pituitary adenoma	88	28.7
Astrocytic and oligodendroglial tumours	63	20.5
Craniopharyngioma	12	3.9
Embryonal tumours	12	3.9
Ependymoma	7	2.3
Tumours of the cranial nerves	6	2.0
Choroid plexus tumours	4	1.3
Lymphoma	1	0.3
Tumours of the pineal gland	1	0.3
Total	*307*	

Only six metastatic intracranial tumours were diagnosed within the study period.

Null cell adenomas were the most common subtype (Figure 3), occurring in 32 (45.7%) with a mean age of 48.81±11.06 years (Tables II and III). This subtype had a male-to-female ratio of 1.9:1 (Table II). They were also seen primarily in patients in their fifth decade of life (Table IV). Gonadotrophs were the second most common adenomas (all stained positive for FSH-beta immunostain) (Figure 1). These occurred in 16 (22.9%) cases (Table III and Figure 3). The mean age in this subtype was 47.5±14.07 years, with an equal male-to-female ratio of 1:1 (Table II). They were most commonly seen in patients in their sixth decade (Table IV).

Lactotroph adenomas occurred in 12 (17.2%) pituitary adenoma cases (Table III and Figure 3). The mean age of the patients with this subtype was 34.16±13.91 years, with a male-to-female ratio of 3:1 (Table II). Their peak age group was the third decade of life (Table IV). Somatotroph adenomas occurred in 4 (5.7%) of all adenomas (Table III and Figure 3). The mean age of the patients with this tumour type was 30.75±13.30 years, with a male-to-female ratio of 1:1 (Table II). This subtype had an equal distribution per decade between the second and fifth decades of life (Table IV).

Plurihormonal adenomas accounted for 5.7% (n = 4; GH+PRL+ACTH = 3, PRL+TSH+FSH = 1) of adenoma cases (Table III and Figure 3). The mean age of the patients was 26.5±12.66years, with a male-to-female ratio of 3:1 (Table II). Plurihormonal adenomas were most prevalent in the second decade of life (Table IV). Thyrotroph and corticotroph adenomas were the least common subtypes of pituitary adenomas, each occurring in one (1.4%) case each (Table III and Figure 3). They were females in their fifth decade of life (Tables II and IV). There was no case of double adenoma or LH-gonadotroph pituitary adenoma immunophenotype.

Only six (8.75%) cases occurred in the paediatric age group. Their ages were between 11 years and 18 years (Figure 1 and Table 4). The male-to-female ratio within this age group was 2:1. The adenoma hormonal subtypes in these children were lactotroph adenomas (n = 2), plurihormonal adenoma (n = 2), somatotroph adenoma (n = 1), and gonadotroph adenoma (n = 1).

Table II: Age and gender distribution of pituitary adenoma cases and their immunophenotypes analysed in the study

	Total Number	Percentage	Age: Mean (SD)	Age: Median	Age: Mode	Age: Minimum	Age: Maximum	Age: Range	Age: IQR (Q1-Q3)
Somatotroph adenomas									
Male	2	50.0	43 (±7.07)	43	N/A	38	48	10	5 (40.5-45.5)
Female	2	50.0	20.50 (±3.53)	20.5	N/A	18	23	5	2.5 (19.3-21.8)
Total	4	100.0	30.75 (±13.30)	28.5	N/A	18	48	30	15.7 (21.8-37.5)
Lactotroph adenomas									
Male	9	75.0	32.11 (±14.68)	25	N/A	17	59	42	17 (22-29)
Female	3	25.0	40.33 (±11.24)	43	N/A	28	50	22	11 (35.5-46.5)
Total	12	100.0	34.16 (±13.91)	31	23	17	59	42	20.5 (24.3-44.8)
Gonadotroph adenomas									
Male	8	50.0	44.9 (±14.63)	48.5	N/A	15	60	45	15.3 (38.5-53.8)
Female	8	50.0	50.1 (±13.94)	52	57	30	68	38	18.25 (40.75-59)
Total	16	100.0	47.5 (±14.07)	48.5	47	15	68	53	19 (38.5-57.5)
Null cell adenomas									
Male	21	65.6	49.95 (±10.28)	48	47	31	69	38	13 (43-56)
Female	11	34.4	46.64 (±12.64)	49	62	25	62	37	18 (39-57)
Total	32	100.0	48.81 (±11.06)	48.5	47	25	69	44	14.5 (41.8-56.3)
Plurihormonal adenomas									
Male	3	75.0	28.66 (±14.57)	27	N/A	15	44	29	14.5 (21-35.5)
Female	1	25.0	20	20	N/A	20	20	20	N/A
Total	4	100.0	26.5 (±12.66)	23.5	N/A	15	44	29	12.5 (18.75-31.25)
Thyrotroph adenomas (n = 1; female; age = 42 years)									
Corticotroph adenomas (n = 1; female; age = 43 years)									
Total Pituitary Adenoma Cases									
Male	43	61.4	43.65 (±14.92)	47	47	15	69	54	18 (35-53)
Female	27	38.6	43.25 (±13.01)	43	43	18	68	50	24.5 (32-56.5)
Total	70	100	43.51 (±14.20)	45	43	15	69	54	20.75 (34-54.75)

N/A - Not applicable

The clinical presentations were available for only 51 of the 70 patients. The commonest presenting feature was visual loss/deterioration (84.3%) (Table V). Other clinical features included headache (47.1%), infertility (11.8%), galactorrhea (7.9%), acromegaly (5.9%), gynaecomastia (5.9%), loss of libido (5.9%), amenorrhea (3.9%), erectile dysfunction (3.9%), memory loss/forgetfulness (3.9%), increased urinary frequency (1.96%), ptosis (1.96%), altered sensorium with seizures (1.96%), cold intolerance (1.96%), obstructive hydrocephalus (1.96%), weight loss (1.96%), and early menopause (1.96%) (Table V).

Most cases (46; 65.7%) were macroadenomas with sizes ranging from 1.0 cm to 4.0 cm in their largest diameter (Table III). Eighteen (25.7%) pituitary adenomas were giant (Table III). In addition, a substantial proportion (13; 40.6%) of the null cell adenomas were giant adenomas with sizes greater than 4cm (Table III). Only eight invasive adenomas (5 macroadenomas and three giant adenomas) were recognized using radiologic imaging (MRI).
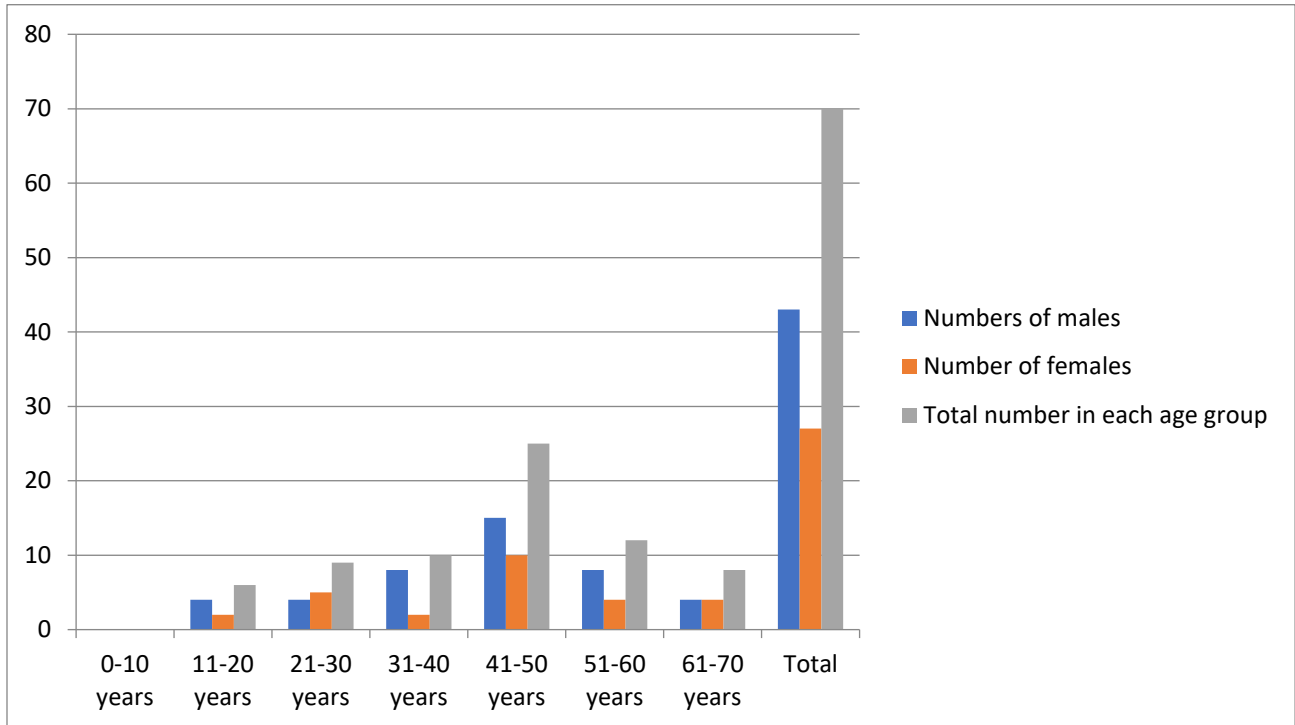

Figure 1: Bar chart showing age-group and gender distribution of pituitary adenoma cases
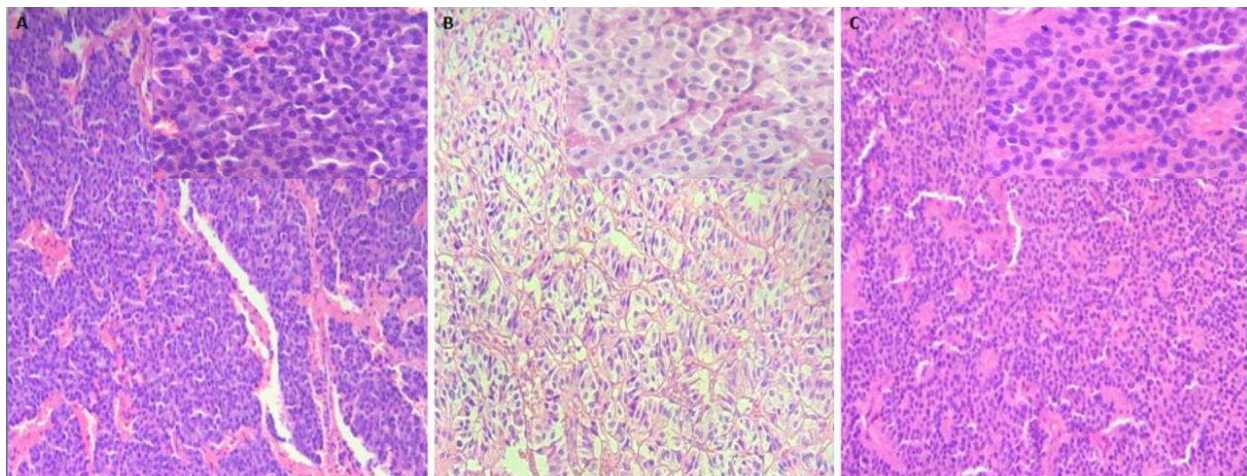
Figure 2: Photomicrographs (Haematoxylin& Eosin stain) of the pituitary adenoma tissues seen in the study. A. Basophilic adenoma (magnification x 100, inset x 400) B. Chromophobic adenoma (magnification x 100, inset x 400). C. Acidophilic adenoma (magnification x 100, inset x 400).

Table III: Distribution and tumour sizes of the hormonal immunophenotypes of pituitary adenoma cases

Adenoma type	Immunophenotype	n (%)	Tumor size <1cm	Tumor size 1-4cm	Tumor size >4cm
Somatotroph adenoma	GH±PRL	4 (5.7)	n = 1 (25)	n = 3 (75%)	n = 0 (0%)
Lactotroph adenoma	PRL, PRL+GH (focal or inconstant)	12 (17.2)	n = 0 (0.0)	n = 10 (83.3%)	n = 2 (16.7%)
Thyrotroph adenoma	TSH-beta, alpha subunit	1 (1.4)	n = 0 (0.0)	n = 1 (100%)	n = 0 (0%)
Corticotroph adenoma	ACTH	1 (1.4)	n = 1 (100.0)	n = 0 (0%)	n = 0 (0%)
Gonadotroph adenoma	FSH-beta	16 (22.9)	n = 0 (0.0)	n =13 (81.3%)	n =3 (18.75%)
Null cell adenoma	No markers	32 (45.7)	n = 2 (6.3)	n = 17 (53.1%)	n = 13 (40.6%)
Plurihormonal adenoma	GH+PRL+ACTH (n = 3) PRL+TSH+FSH (n = 1)	4 (5.7)	n = 2 (50.0)	n = 2 (50%)	n = 0 (0%)
Total		*70 (100.0)*	*n = 6 (8.6)*	*n = 46 (65.7)*	*n = 18 (25.7)*

No double adenoma or LH-gonadotroph pituitary adenoma immunophenotype was seen in the study.

Table IV: Age distribution of the hormonal immunophenotypes of the pituitary adenoma cases

Adenoma type	Age: 0-10 years	Age: 11-20 years	Age: 21-30 years	Age: 31-40 years	Age: 41-50 years	Age: 51 - 60 years	Age: 61-70 years
Somatotroph adenoma	0	1	1	1	1	0	0
Lactotroph adenoma	0	2	4	2	1	3	0
Thyrotroph adenoma	0	0	0	0	1	0	0
Corticotroph adenoma	0	0	0	0	1	0	0
Gonadotrophadenoma	0	1	1	3	4	5	2
Null cell adenoma	0	0	2	4	14	6	6
Plurihormonal adenoma	0	2	1	0	1	0	0

Only 25 (35.7%) of the 70 pituitary adenoma cases had pre-operative serum hormonal levels available. Of these 25 cases, 17 (68%) were functional (secreting) adenomas with elevated preoperative serum hormonal levels. These functional adenomas consisted of 6 null cell type adenomas (1 adenoma, 3 macroadenomas, and 2 giant adenomas), 5 FSH-gonadotrophs (4 macroadenomas and 1 giant adenoma), 3 lactotrophs (1 macroadenoma and 2 giant adenomas), 1 corticotroph (macroadenoma), 1 thyrotroph (macroadenoma), and 1 plurihormonal adenoma (giant adenoma). All the

non-prolactinomas also had mildly elevated preoperative serum prolactin levels, which could be attributed to pituitary stalk compression syndrome.

Thirteen (25.5%) of the 51 pituitary adenoma cases with available clinical information were non-functional/silent adenomas. Of these 13 silent adenomas, 6 were FSH-gonadotrophs (4 macroadenomas, and 2 giant adenomas), 4 were lactotrophs (all macroadenomas), 2 were plurihormonal adenomas (one adenoma and one

macroadenoma), and 1 was a somatotroph adenoma (macroadenomas).

Only one case of pituitary apoplexy (sudden haemorrhage into pituitary adenoma) in a null cell non-functional macroadenoma was recorded.

Only 28 of the 70 pituitary adenoma cases had records of post-operative follow-up clinical. Of these 28 patients, 18 had improved pre-operative

symptoms. Most patients (n=18) reported improved vision, 5 had persistent visual impairment, 6 had tumour recurrence, 3 had post-surgical complications of diabetes insipidus with secondary adrenal insufficiency, including polyuria and hyponatremia, and 1 died four days postoperatively. Five recurrent adenomas (83.4%) were null cell types, while 1 was a prolactinoma.
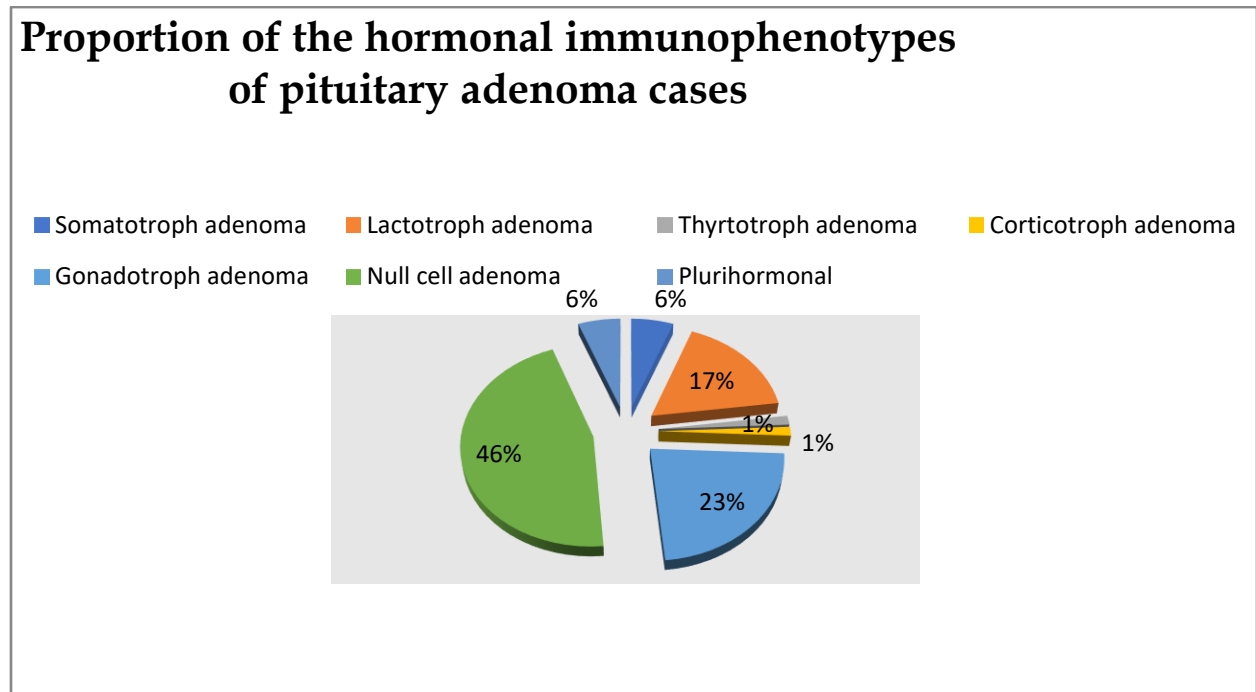
Figure 3: Distribution of the hormonal immunophenotypes of the pituitary adenoma cases

Discussion

Pituitary adenoma was the second most common primary intracranial tumour in this study. This finding is similar to some studies in Nigeria. [7-11] It, however, contrasts with global reports and some other reports from studies done in Nigeria, where pituitary adenoma was the third most common primary intracranial tumour. [1,2-6]

The male-to-female ratio of pituitary adenoma in the present study was 1.6:1. This is consistent with reports by Nwokoro *et al.* [25] and Matthew

et al. [26] with male-to-female ratios of 1.2:1 and 1.3:1 respectively. The present study is also consistent with the reports of Heshmat *et al.*, in which a higher incidence of pituitary adenomas in males in both Caucasians and Blacks was reported. [27] However, this is incongruent with the slight female preponderance reported by Salami *et al.* in 2013 in Ibadan, Nigeria.[24] The finding is also slightly different from studies by McDowell *et al.* [28] and Hemminki *et al.* [29], where male rates were higher among older persons, but female rates were higher among younger persons. The discordance in the male-to-female

ratio in their study compared to the present study may be because their studies were cancer registry-based. In addition, some of the pituitary adenomas in our environment, especially prolactinomas commoner in females, may have been treated with medications, thus escaping histological diagnosis.

The report by Salami *et al.* [24] in Ibadan of an overall peak age of pituitary adenoma occurrence in the fifth decade of life is also similar to our findings. However, Salami *et al.* [24] reported different peak ages of pituitary adenoma for males and females - they were the sixth and fourth decade of life, respectively. Gruppetta *et al.* [30] reported the frequency of pituitary adenomas to be highest between 40 and 60 years of age, similar to the present study's findings (41-50 years). Similarly, Matthew *et al.* [26] also reported the fourth to sixth decade of life as the peak incidence of pituitary adenoma.

Table V. Clinical presentations of the pituitary adenoma cases

Clinical presentations	*Total* n	Somatotroph n	Lactotroph n	Thyrotroph N	Corticotroph n	Gonadotroph n	Null cell n	Plurihor monal n
Visual loss/ deterioration	43	3	6	1	0	10	21	2
Headaches	24	2	4	1	1	5	9	2
Infertility	6	0	1	0	0	2	2	1
Galactorrhea	4	0	0	0	0	2	1	1
Acromegaly	3	1	1	0	0	0	1	0
Gynaecomastia	3	0	0	0	0	3	0	0
Loss of libido	3	0	0	0	0	1	1	0
Amenorrhea	2	0	0	0	0	1	1	0
Erectile dysfunction	2	0	0	0	0	2	0	0
Memory loss/ forgetfulness	2	0	0	0	2	0	0	0
Ptosis	1	0	1	0	0	0	0	0
Increased urinary frequency	1	0	0	0	1	0	0	0
Altered sensorium and seizures	1	0	0	0	0	1	0	0
Cold intolerance	1	0	0	0	0	0	0	1
Obstructive hydrocephalus	1	0	0	0	0	0	1	0
Weight loss	1	0	0	0	0	0	1	0
Early menopause	1	0	0	0	0	0	1	0

The photomicrographs of the pituitary adenoma immunophenotypes are shown in Figure 4.
The mean and median ages of pituitary adenoma in several studies carried out in Nigeria ranged between 42 years and 45 years. [24, 25, 27] This concurs with the present study's findings. The age and sex distribution of pituitary adenoma subtypes are disparate in various studies. [31]

The present study observed paediatric cases in only 8.75% of the pituitary adenoma cases. This finding is similar to that of Salami *et al.* [24] where 8.51% of the pituitary adenoma cases studied were patients under the age of 18 years. These findings align with the general report of pituitary adenoma, which is uncommon in childhood and adolescence. However, there may be a slight increase during puberty, especially in girls with

prolactinomas and boys with somatotroph adenomas. [32-34]

Prolactin-producing adenomas (prolactinomas) are the most common hormone-producing PitNETs/PA in adults and children worldwide. [23] However, the most common pituitary adenoma hormonal phenotype reported in several studies done in Nigeria is the null cell subtype, as also observed in our study. [24, 25] The findings in the present study agree with Salami *et al.*'s report [24] that the three common phenotypes are the null cell type, the gonadotrophs and the lactotrophs. LH adenomas are rare worldwide [35]; hence, it is unsurprising that there was no LH adenoma in the present study.
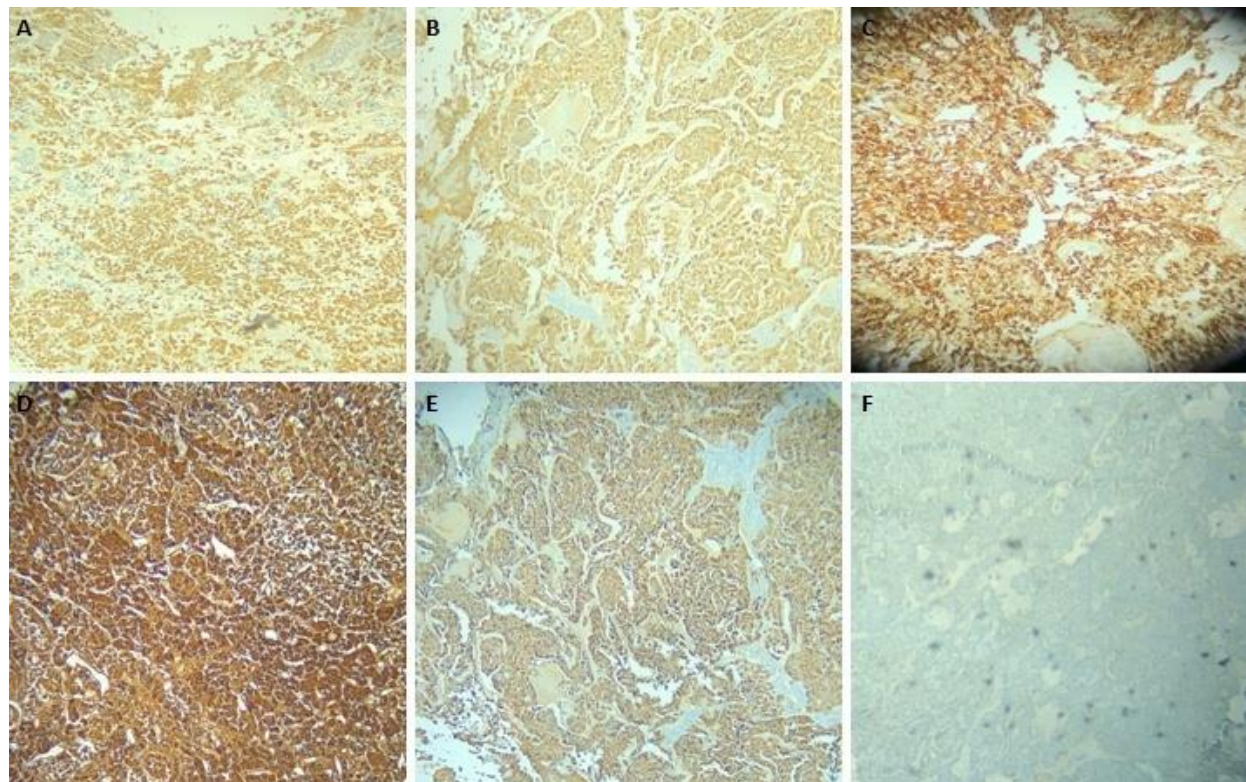
Figure 4. Photomicrographs of immunophenotypes of the pituitary adenomas seen in the study. A. GH (x 40 magnification). B. Prolactin (x 40 magnification) C. ACTH (x 40 magnification). D. TSH (x 40 magnification). E. FSH (x 40 magnification) F. LH (x 40 magnification).

Most (65.7%) of the adenomas in this study are macroadenomas, while 25.7% were giant adenomas. Similar findings were reported by Matthew *et al.* [26] However, the majority of the giant macroadenomas reported were plurihormonal adenomas and not null cell adenomas as reported in the present study.[26] Matthew *et al.* [26] also reported recurrent rates of 5 out of 29 cases, similar to the finding in the present study (6 out of 28 cases). [26] The majority of the recurrent cases in the present study were null cell adenomas. This contradicts the findings reported by Matthew *et al.* [26] where the majority were plurihormonal adenomas. [26]

Most of the patients in this study presented with clinical features indicative of increased intracranial pressure and mass effect, such as visual deficit and headache suggestive of late clinical presentation. These findings are similar to studies by Matthew *et al.* and Cury *et al.* [26,36] Studies have shown that the prevalence of the different histologic subtypes of non-functional pituitary adenomas (NFPAs) depends on the

extent of their immunohistochemical profile. [37] A large retrospective case series by Nishioka *et al.* showed gonadotroph adenoma as the most common NFPA subtype, followed by the corticotrophs, the PIT1 plurihormonal (GH/PRL/TSH) lineage, and null cell adenomas. [38] This finding is similar to the present study, as most of the non-functional/silent adenoma cases in this study were gonadotrophs. However, our study's second most common NFPAs were the lactotrophs, followed by plurihormonal and somatotrophs (7.7%). Plurihormonal adenomas are the commonest immunohistotype of pituitary adenoma to recur, according to the literature.[35] However, most of the recurring adenomas in the present study were null-cell adenomas and only one plurihormonal adenoma was noticed to recur.

Limitation

It is acknowledged that the present study only included the pituitary adenoma cases for which surgery and histology were performed in one health facility. As such, the findings may differ from those of the general population. In addition, hormonal immunohistochemistry was employed to classify pituitary adenoma cases according to the 2014 WHO classification of pituitary tumours. Immunoreactivity to transcription factors was not performed. The number of null cell adenomas in this study might have been lower if the immunohistochemistry for transcription factors had been performed.

Conclusion

The pituitary adenomas seen in this study have a male preponderance with most being macroadenomas. The null cell adenoma and visual impairment are the commonest hormonal phenotype and presenting features of pituitary adenoma in this study.

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