

1. INTRODUCTION

Pituitary tumours are common, estimated to constitute 10 to 15% of all primary brain tumours. They have been studied extensively in the developed world. To the author's knowledge, pituitary adenomas have never been analyzed in our institutions before.

The author intends to review the records of patients presenting with pituitary adenomas at the Chris Hani Baragwanath and Charlotte Maxeke Johannesburg Academic Hospitals starting from 1999 to 2008. The demographical distribution consisting of age, sex and race of the patients will be studied. Further more, clinical presentation, specifically with regard to visual deficits such as loss of visual acuity and field defects will be looked into, along with development of headaches and symptoms of hormonal disturbance.

The type of tumour with regard to histology, radiological grading and pituitary hormone deficiencies or excesses will be analyzed.

Lastly the management and outcome of the patients treated at our institutions will be critically looked into and assessed. The findings of our study will then be compared to those in the published literature.

Furthermore, we will use the findings of this study to assess our management protocols and outcome.

1.1 Literature Review

1.1.1 Demographics

Pituitary tumours are not uncommon. They comprise 10-15% of all primary brain tumours ^(1, 2, 3). About 20-30% of pituitary tumours are detected accidentally ⁽¹⁾ with imaging for unrelated indications, that is the so-called incidentalomas ⁽⁴⁾. The prevalence of incidentalomas in autopsy series is as high as 20-25 % ⁽¹⁾. However, their clinical prevalence has been estimated at 0, 02 % ⁽⁵⁾.

While the overwhelming majority of pituitary tumours are sporadic, 5% occur in the setting of a hereditary syndrome either as part of multiple endocrine neoplasia (MEN-1) or Carney complex (CNC) ⁽²⁾.

Though pituitary tumours occur in virtually all age groups, the peak incidence is between the third and sixth decades ⁽¹⁾. Functioning pituitary adenomas are more prominent in younger patients while non functioning adenomas occur commonly in older patients. Pituitary adenomas are very rare in paediatric age groups, representing only 2% of all primary paediatric brain tumours ⁽¹⁾.

Most series indicate that young women are affected more frequently, even though incidentalomas are evenly distributed among the sexes in autopsy series ⁽¹⁾. Corticotropinomas are an exception. Female to male ratio of ACTHomas is 4:1 ⁽⁶⁾.

In one study of 516 patients, the gender distribution was 43, 3% male and 56,7% female ⁽³⁾. The reason for this apparent discrepancy is probably on the basis of menstrual irregularities and infertility which young women are likely to suffer, thus their early presentation ⁽³⁾. However, another study had 63% being male patients ⁽⁷⁾. No racial predilection exists for pituitary adenomas ⁽⁶⁾.

1.1.2 Clinical Presentation

Patients with pituitary tumours may be asymptomatic or may present with symptoms of hormonal imbalance and or mass effect ⁽⁶⁾.

The mass effects of pituitary adenomas include headaches, visual disturbance, intracranial haemorrhage and increased intracranial pressure ⁽⁶⁾. The most frequent symptom on admission is visual disturbance, including bitemporal hemianopsia (62%), unilateral temporal hemianopsia (26%), bitemporal quadrantanopsia (14%), optic atrophy and loss of visual acuity (39%) ⁽⁵⁾. The above symptoms occur as a result of direct compression of the optic apparatus by the tumour mass ⁽⁶⁾. Cavernous sinus involvement manifests as extraocular cranial nerve palsies in 9, 6% of patients with visual disturbance ⁽³⁾.

One study revealed that 60% of patients present with headaches and or visual symptoms, 12% with apoplexy and 28% with pituitary hyper function. In this study 55% of the tumours were functioning while 44% were non-functioning adenomas ⁽⁷⁾.

The following clinical syndromes are the result of hormonal hyper/hypo secretion by the tumour:

- Hyperprolactinaemia presents with infertility, amenorrhoea, oligomenorrhoea and/ or galactorrhoea in females (40, 3%) ^(3,6). Male patients present with loss of libido and impotence (14, 2%) ⁽³⁾.
- 22% of patients present with acromegaly or gigantism as a result of excess secretion of growth hormone by a somatotropinoma, usually a macro-adenoma. Inadequate growth hormone secretion result in failure to thrive in children, but is often asymptomatic in adults ⁽⁶⁾.
- Thyrotropin excess presents with symptoms of secondary hyperthyroidism while gonadotropinomas are usually asymptomatic.

- Gonadotropinomas are usually macroadenomas and may result in hypopituitarism. Rarely, they can result in testicular enlargement in males and ovarian hyper stimulation in females. Deficiency of gonadotrophins presents with hypogonadism and infertility.
- Corticotropin excess result in Cushing's disease. These tumours are commonly micro-adenomas. Corticotropin suppression due to compression of the normal corticotrophins present with glucocorticoid insufficiency⁽⁶⁾.

Pituitary apoplexy is an uncommon event⁽³⁾. It results from infarction of a pituitary tumour or sudden haemorrhage within the pituitary gland⁽⁶⁾. This presents as a medical emergency with a severe headache, sudden collapse, shock and death if not treated emergently. Other symptoms include deterioration of visual acuity, weakness of ocular motility and symptoms of endocrine dysfunction^(8,9,6).

A rare case of internal carotid artery occlusion accompanied by hemiplegia, lethargy, sudden headache and visual disturbance has been reported⁽²⁹⁾.

With regard to pregnant patients, galactorrhoea, headaches, seizures and blurring of vision were found to be common presenting features. The same study could not however elicit any significant difference in infertility and menstrual disorders between patients with macroadenomas and micro adenomas. Macroadenomas were however associated with lower birth weight and increased rate of caesarean delivery⁽¹⁰⁾.

Nelsons syndrome occurs as a result of bilateral adrenalectomy. The lack of negative glucocorticoid feedback is postulated to lead to excessive pituitary tumour growth. Such tumours are much more aggressive and locally invasive compared to the usual corticotrophin adenoma.

1.1.3 Differential Diagnosis of a sellar mass ^(1,15,6)

- Tumours of adenohypophyseal origin
 - Pituitary adenoma
 - Pituitary carcinoma

- Tumours of neurohypophyseal origin
 - Astrocytomas
 - Granular cell tumour

- Tumours of non-pituitary origin
 - Craniopharyngioma
 - Germ cell tumours
 - Gliomas
 - Meningiomas
 - Chordomas

- Cysts, hamartomas and malformations
 - Rathke's cleft cyst
 - Arachnoid cyst
 - Epidermoid cysts
 - Dermoid cysts
 - Hypothalamic hamartomas
 - Empty Sellar Syndrome

- Metastatic Tumours e.g.
 - Carcinomas
 - Plasmacytomas
 - Lymphoma
 - Leukemia

- Inflammatory conditions
 - Pyogenic infections or abscess
 - Granulomatous infections
 - Mucocoele
 - Lymphocytic hypophysitis
 - Sarcoidosis
 - Langerhans cell histiocytosis
 - Giant cell granuloma

- Vascular lesion
 - Saccular aneurysms
 - Cavernous angioma

1.1.4 Aetiology/molecular biology

The causes of pituitary adenomas are unknown. The most favoured hypothesis is that of neoplastic transformation of monoclonal pituitary cells. This theory is suggested by the monoclonal nature of most pituitary tumours and their retention of a response to negative feedback by hormones produced by target organs⁽⁶⁾.

There is a deletion of a tumour suppressor gene on chromosome 11 in tumours associated with MEN-1 Syndrome⁽¹¹⁾. 30-40% of somatotrophic tumours have a mutation in the gsp oncogene which codes for the alpha subunit of Gs, elevation of intracellular GMP seems to play a role in secretory activity⁽⁶⁾. Loss of negative feedback by target gland as seen in thyrotropinomas and gonadotropinomas suggest that pituitary adenomas arise as a result of target gland or hypothalamic dysregulation⁽¹²⁾.

1.1.5 Pathology

Pituitary gland is a bilobed structure, consisting of an anteriorly located adenohypophysis in apposition with a morphologically, embryologically and functionally distinct posterior neurohypophyseal component ^(1,6). Tumours arising from the neurohypophysis are rare and consist of gliomas, granular tumours, hamartomas and metastatic tumours. Majority of pituitary tumours arise from the adenohypophysis mainly in the form of histologically benign adenomas ⁽¹⁾. Macroscopically pituitary adenomas are yellowish-gray to purple and are usually soft and creamy as opposed to the firm normal gland ⁽¹⁾.

As mentioned above, pituitary adenomas are benign tumours arising from the adenohypophysis ⁽⁴⁾. Histological classification is based on the staining properties of the cell cytoplasm when viewed under light microscopy and immunocytochemistry, revealing the secretory patterns of the tumour ⁽¹¹⁾.

The immunocytochemistry technique uses antibodies directed against each of the pituitary hormones to positively stain cells expressing them. A normal pituitary gland has a mixture of different cell types while an adenoma has a large group of cells with similar hormone expression ⁽²⁾. Pituitary adenomas can be classified according to functional, radiologic or histological criteria ⁽²⁾.

Histologically, they are characterized by cellular monomorphism and lack of acinar organization. On the other hand, normal pituitary gland exhibits an admixture of different cell types arranged in a well organized acinar pattern ⁽¹⁾. Smears of adenomatous tissue are cell rich, whereas those of normal pituitary are paucicellular. Cytological monomorphism, uniform cytoplasmic staining, multinucleate or pleomorphic cells, prominent nucleoli, or mitotic figures favour a diagnosis of adenoma ⁽¹⁾.

Folate Receptor (FR- α) is significantly over expressed in non-functional tumours⁽¹⁴⁾. FR- α is capable of binding folate and thus mediates in vitamin uptake and tumour growth⁽¹⁴⁾.

1.1.6 Laboratory Results

Laboratory results may indicate either hyper, hypo or normal secretion of hormones^(1,15). The most common increased hormone abnormality is hyperprolactinaemia, which was reported as 64% in one study, followed by increased growth hormone (20%), adrenocorticotrophic hormone (ACTH) (6,7%), follicle stimulating hormone-lutenising hormone (FSH-LH) (3,1%) and mixed hormone excess in 2,2%⁽¹⁴⁾. The majority of mixed hormone excess was found to involve both growth hormone and prolactin levels in the above study.

Tests routinely performed to assess pituitary function include: Thyroid function tests (TFT), baseline a.m plasma cortisol and response to ACTH, LH and FSH, testosterone in men, prolactin, growth hormone (GH) and insulin like growth factor-1 (IGF-1).

Prolactin levels rise shortly after conception to reach levels of 150-200ng/ml at term. Normal prolactin levels are less than 15ng/ml in men and less than 20ng/ml in non-pregnant females. Other causes of hyperprolactinaemia include stress, hypoglycaemia, renal failure, hypothyroidism and phenothiazine like medications⁽¹⁴⁾.

Growth hormone is secreted in a pulsatile fashion resulting in between two and seven peaks per 24 hours. Although bursts of GH secretion are associated with meals, much of the GH secretion occurs during sleep. GH has a half life of 20-30 minutes. Thus GH levels vary considerably in a 24hour period. Somatomedin C, also known as IGF-1, is produced by the liver in the presence of growth hormone and has a half life of 3-18 hours. Thus IGF-1

levels provide a more reliable indication of the exposure of the body to GH than does a random determination of GH ⁽¹⁴⁾.

Normal base GH levels are less than 1ng/ml. Acromegalics have basal levels above 5ng/ml, although some patients may have normal basal levels with elevations only during secretory bursts ⁽¹⁴⁾.

IGF-1 levels are however constant throughout the day and are consistently elevated in acromegaly and gigantism. Thus, static measurements of IGF-1 are an effective and reliable method of confirming the diagnosis of acromegaly ⁽¹⁴⁾.

An alternative means of confirming the presence of acromegaly involves the performance of a glucose tolerance test. Under normal circumstances, GH suppresses to a level below 1ng/ml after an oral glucose load of (100g). In acromegaly, the GH level fails to suppress following a glucose load ⁽¹⁴⁾.

While Cushing's syndrome is usually easy to recognize clinically, it can be difficult to define aetiologically. Plasma and urinary cortisol can be measured basally and in response to dexamethasone or metyrapone, as well as determination of plasma ACTH may help in determining the source of the hypercortisolaemia ⁽¹⁴⁾.

Cortisol is released in a diurnal pattern, with the highest levels in the morning and lowest levels in the evening. Cortisol levels also increase in response to stress, physical or metabolic ⁽¹⁴⁾.

If the above are equivocal, corticotropin releasing hormone (CRH) measurements and CRH stimulation testing with measurements of ACTH and/or cortisol peripherally or from the petrosal sinuses are now employed to provide additional evidence in the diagnosis of Cushing's disease ⁽¹⁴⁾.

Glycoproteins tested include thyroid stimulating hormone (TSH), FSH and LH. Most of the so-called non-functioning adenomas actually have been proven to secrete FSH and LH by immunohistochemistry ^(2,13,14)

1.1.7 Imaging

The imaging studies include Magnetic Resonance Imaging (MRI), computed tomography (CT), angiography and plain X-Rays. Pneumoencephalogram used to be used but it is no longer relevant in this MRI/CT era ⁽³⁾.

MRI is acknowledged to be the best radiological test for pituitary tumours ⁽¹⁶⁾. Due to its multiplanar and three dimensional imaging capabilities, vascular imaging capabilities and thin collimation, high field MRI is able to demonstrate the size of the tumours including supra and parasellar extension, the relationship of the tumour to the surrounding structures such as optic apparatus, cavernous sinus, internal carotid artery and its branches and sphenoid sinus. Post operative residual and recurrent tumours are also well demonstrated by MRI ^(16,12).

Pituitary adenomas are usually iso-intense to surrounding brain matter on T1 weighted images. Due to lack of blood brain barrier, the normal pituitary gland, along with the infundibulum and the cavernous sinuses enhance with contrast material. In delayed images, the adenoma will enhance long after the normal pituitary gland has washed out the contrast material ⁽¹²⁾.

Coronal and sagittal T1-weighted images with and without gadolinium best define the sellar anatomy and its relationships mentioned above ⁽¹⁵⁾. This technique can identify up to 70% of micro adenomas, including those as small as 3mm in diameter ⁽¹⁾.

CT has generally been superseded by MRI. It is useful where MRI is not available or is contraindicated e.g. in a patient with a pacemaker. The CT pictures must include coronal views through the sellar turcica. CT angiography may be performed to lay out parasellar carotid arteries. Calcium in the sellar signifies haemorrhage or infarction in the tumour^(12,17).

Lateral skull X-Rays may help define anatomy of the sphenoid sinus in cases where transphenoidal surgery is contemplated⁽¹⁷⁾.

Angiography is rarely required since MRI reveals the position of the carotid arteries as areas of flow void. Angiography may reveal variable lateral displacement of the cavernous carotid arteries and superior displacement of the proximal portions of the anterior cerebral arteries⁽¹⁸⁾. Since patients with large pituitary adenomas may have hypo-cortisolaemia, it is important to administer 100mg of intravenous hydrocortisone prior to angiography to prevent the patient from becoming hypotensive⁽¹⁸⁾.

Micro adenomas are 10mm or smaller in diameter while macroadenomas are greater than 10mm in the widest diameter⁽³⁾.

The radiological classification of pituitary adenomas was introduced by Hardy in 1969 and was later complemented by Wilson in 1979^(12,14).

Hardy classification of pituitary tumours

- | | |
|------------|--|
| Grade I: | Micro adenomas (<1cm) without sellar expansion or invasion |
| Grade II: | Macroadenomas (>1cm) and may extend above the sellar; no invasion of the sellar turcica. |
| Grade III: | <ul style="list-style-type: none">- Macroadenomas with localized invasion- Enlargement of the sellar floor- May have suprasellar extension |

Grade IV: - Diffuse invasion and destruction of the sellar

They may be further classified by the degree of supra and parasellar extension

- a) Extension into suprasellar cisterns only
- b) Extension to recesses of the third ventricle
- c) Extension to involve the whole third ventricle
- d) Involvement of cavernous sinus

Aggressive pituitary adenomas are defined as those tumours with massive invasion of the surrounding anatomical structures, namely cavernous sinus, skull base and sphenoid mucosa in addition to rapid growth and giant size⁽¹⁸⁾. Ectopic pituitary adenomas are rarely reported in the nasopharyngeal⁽¹⁹⁾ and suprasellar⁽²⁰⁾ areas.

The invasion of the pituitary adenoma is related to the size of the tumour, as 80% of the giant adenomas (>4cm), 22% of macro adenoma (>10mm) and only 2% of the micro adenomas (<10mm) invade the surrounding structures⁽¹⁸⁾. One study reported the right cavernous sinus to be two times more likely to be involved than the left⁽¹⁷⁾.

1.1.8 Management

a) History of pituitary surgery⁽¹²⁾

1889 - Sir Victor Horsley performed the first pituitary surgery via transcranial approach.

1907 - Schloffer reported the first successful transphenoidal resection of a pituitary tumour

1909-1910 - Hirsch accessed the sellar through a transseptal

approach using a nasal speculum

- 1910 - Cushing developed the basic oronasal midline rhinoseptal transphenoidal approach
- 1912 - Frazier used the intracranial transfrontal approach to the pituitary.
- 1962 - Hardy refined the transfrontal approach using a Microscope

b) Surgical treatment

The objectives of treatment are to relieve the mass effect, correct the endocrinopathies and control tumour growth.

With the exception of prolactinomas, surgery, using transphenoidal approach (84-90%)^(7,12), though sometimes transcranial (3%)⁽⁷⁾ is the first line of surgical treatment^(13,18). There are various transphenoidal methods including perinasal, paraseptal and endoscopic approaches⁽¹⁸⁾. As mentioned above, the objectives of treatment include decompression of the visual pathways, reduction of hormonal hyper secretion, reduction of the tumour mass and obtaining a definite histological diagnosis^(1,17).

The transcranial approach is useful when the lesion extends beyond the confines of the sellar turcica e.g. into the frontal or middle fossa. In these cases complete excision is very rare with a high recurrence rate⁽¹⁸⁾.

The addition of a transcranial component to the transphenoidal approach offers additional visualization of the critical neurovascular structures during giant pituitary adenoma resection ⁽²¹⁾.

Modern adjuncts to surgery include endoscopic assisted methods, neuronavigation, and intraoperative imaging techniques. These aid orientation and tumour resection but have no effect on tumour recurrence ⁽¹⁸⁾.

In one study, 90% of patients with non-functioning adenomas experienced resolution or improvement in their headaches after transphenoidal surgery ⁽²²⁾. With regard to visual fields and acuity, 35% return to normal, 60% improve and 5% remain unchanged ⁽²³⁾.

In another retrospective study of patients who underwent transphenoidal surgery for excision of pituitary adenomas, 38,8% were found to have developed post operative hyponatraemia ⁽²⁴⁾. 59,2% of these appeared between day 4 and 7 post operatively. They presented with nausea, vomiting, headaches, dizziness, confusion and weakness ⁽²⁴⁾.

Other complications include carotid artery injury, central nervous system injury, haemorrhage, loss of vision, ophthalmoplegia, cerebrospinal fluid leak, meningitis, nasal septum perforation, post operative epistaxis, sinusitis, anterior pituitary insufficiency, diabetes Insipidus and death ^(1,15,25,26).

c) Medical treatment

Medical therapy is indicated for prolactinomas, and as an adjunctive treatment to surgery. It can effectively reduce tumour mass, normalize

hormone hyper secretion and prevent re-expansion in prolactinomas⁽¹⁸⁾.

For prolactinomas, dopamine agonists are the first line of treatment, usually using either cabergoline or bromocriptine^(18,27,28). Cabergoline normalizes hormonal excess associated with prolactinomas in 60-90% of large adenomas^(1,15,18). It is considered superior to bromocriptine because it was shown to normalize prolactin level in 83% of hyperprolactinaemic women vs. bromocriptine in 59%⁽¹⁸⁾. Visual improvement occurs within weeks⁽¹⁸⁾. Side effects of both drugs include headaches, nausea, vomiting, dizziness, vertigo and CSF leak^(1,15,18).

Somatostatin analogues offer therapy for growth hormone releasing adenomas, either as primary therapy, preoperatively to reduce tumour volume or postoperatively to control tumour re-expansion. These include octreotide and lancreatide. Their antiproliferative effects depend on tissue expression of Somatostatin receptors (SSR). They control growth hormone and insulin like growth factor-1 hyper secretion. Their maximal benefits occur after ten years and induce tumour shrinkage in 40-50% of cases when used as primary treatment. They are also used preoperatively to reduce tumour volume and post operatively to control re-expansion⁽¹⁸⁾.

d) Radiation Therapy

Conventional radiation therapy usually consists of 40-50 Gy administered over 4-6 weeks⁽¹⁷⁾. The aim of radiation therapy is local tumour control as well as normalizing the hormone levels⁽⁴⁾. When radiotherapy is combined with surgery, local tumour control is 78% in acromegalics, and 93% in the galactorrhoea-amenorrhoea syndrome⁽⁴⁾.

Side effects include radiation injury to the remaining normal pituitary gland, resulting in hypocortisolaemia, hypogonadism, or hypothyroidism in 40-50% of patients after ten years⁽¹⁷⁾. It may also cause blindness, lethargy, memory disturbance, cranial nerve palsies and tumour necrosis with haemorrhage and apoplexy^(4,17).

2. MATERIALS AND METHODS

The available records of patients presenting to the above mentioned institutions with a presumptive diagnosis of a pituitary adenoma were collected. The information regarding the demographics, clinical presentation, management and outcome were charted in a datasheet using Microsoft excel.

Unfortunately, not all patients' records were available; some were missing completely while others were incomplete. Therefore, patients with missing or incomplete records were excluded from the analysis. About 150 patients were identified and 57 had missing or incomplete records.

2.1 Methodology

The Pearson Chi Square test was used to compare the distributions of categorical variables (e.g. gender, histology etc) of patients at the two sites. The t test was used to compare the distributions of the continuous variable of age (years) of patients at the two sites.

Citation for statistical software

StatSoft, Inc. (2008). STATISTICA (data analysis software system), version 8.0. www.statsoft.com.

3. RESULTS

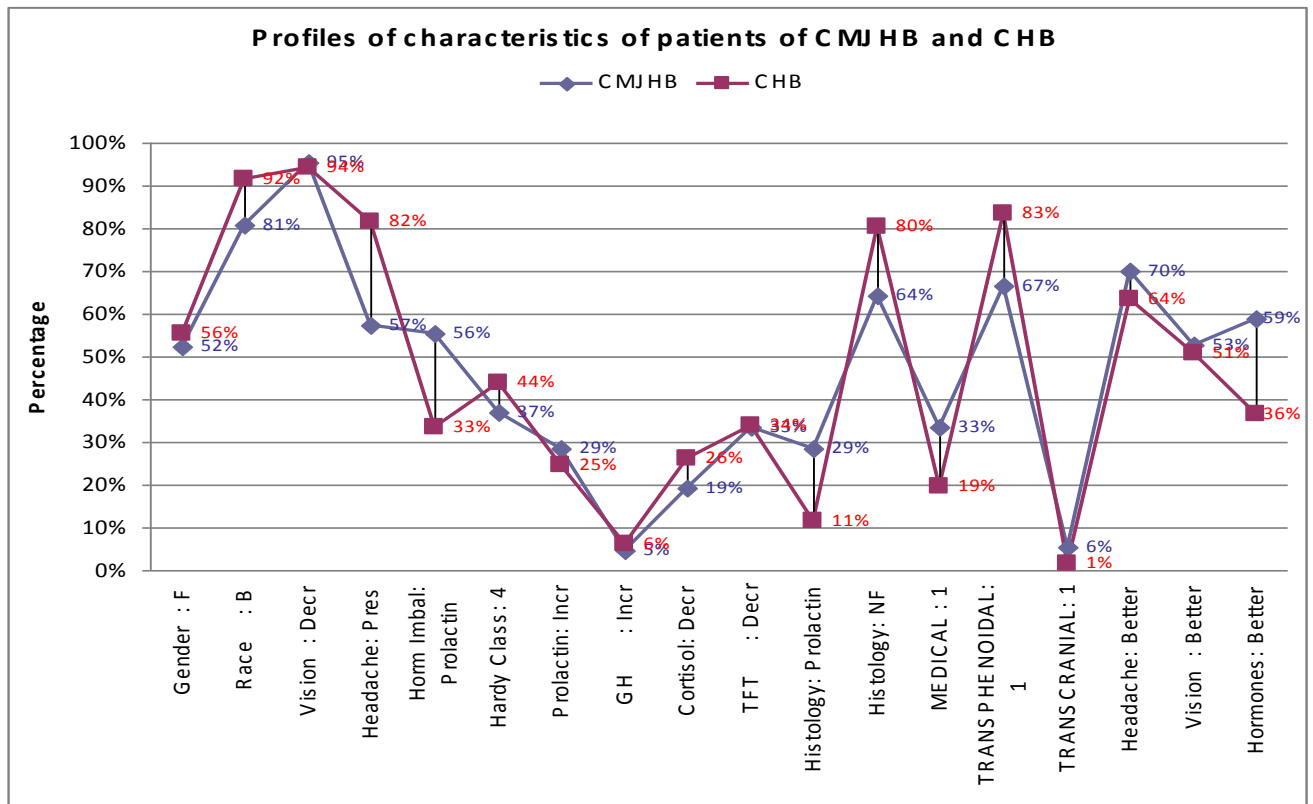


Figure (1). Summary of profiles of characteristics of patients of CMJHB and CHB hospitals.

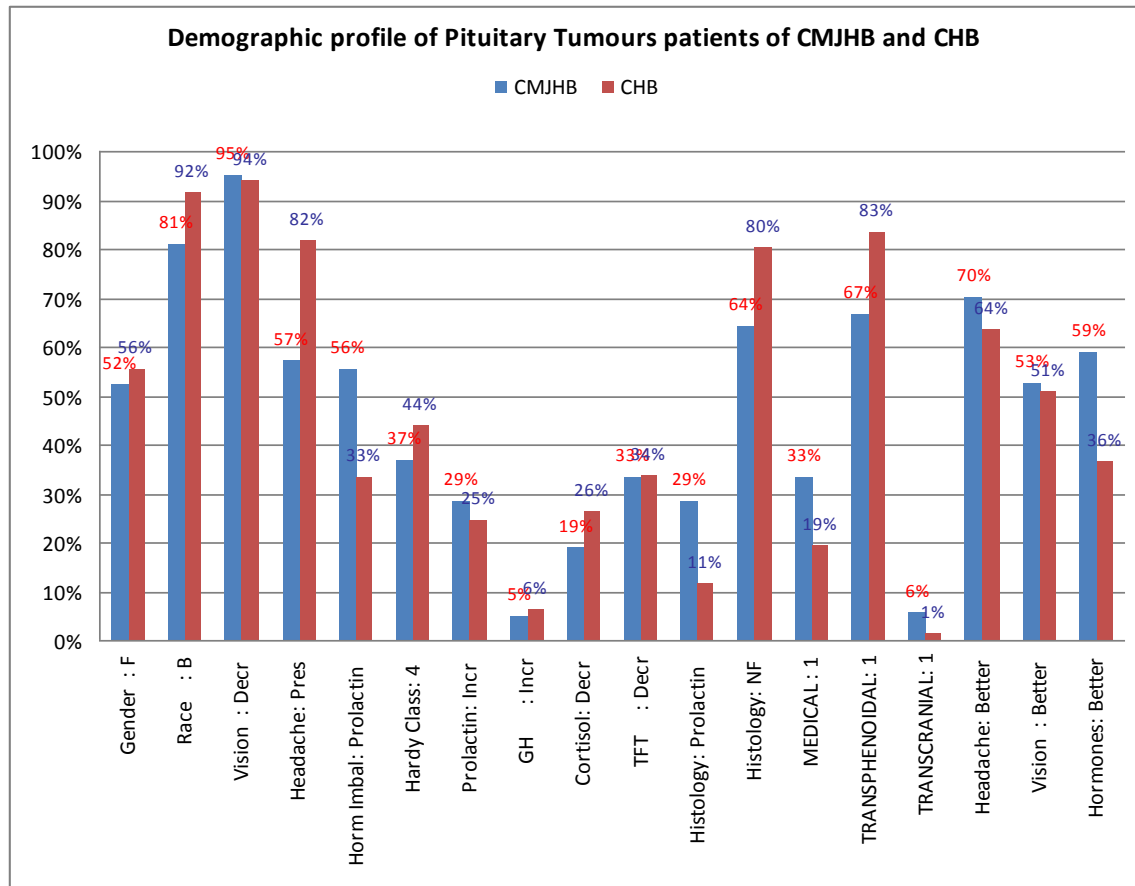


Figure (2). Profile of pituitary tumour patients of CMJHB and CHB hospitals

The above graph and chart illustrate the summarized profiles of patients presenting with pituitary tumours at our institutions over the period of ten years, from 1999 to 2008.

3.1 Age

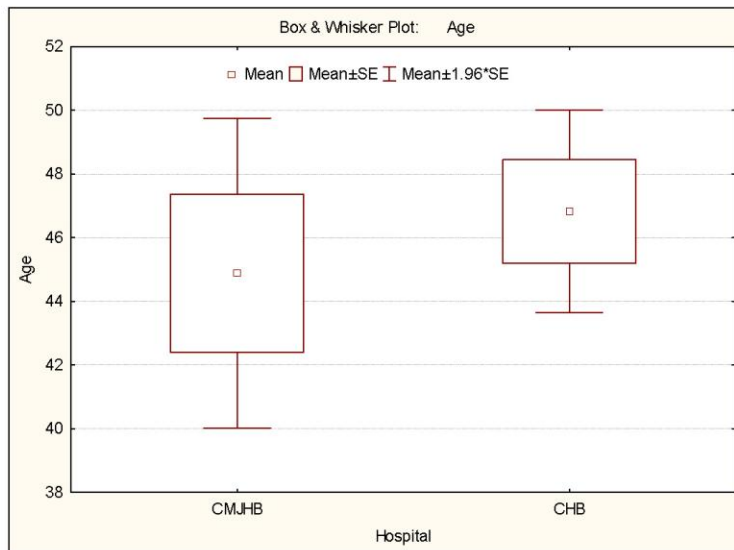


Figure 3. Age distribution of combined groups.

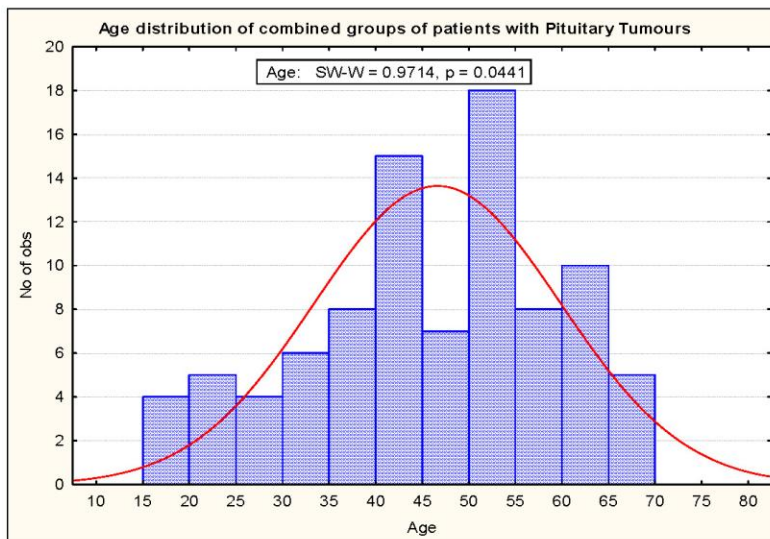


Figure 4. Age distribution of combined groups.

Mean age of patients as indicated above was 44,9 years for CMJA Hospital and 46,8 years for CH Bara Hospital. For prolactinomas, mean age was 40,3 while mean age for non functioning adenomas was 48,6.

There is no significant difference between the age distributions of patients presenting with Pituitary Tumours at CMJHB versus CHB: $t = -0.554$; $df=88$; $p>0.58$. The mean ages of the patients are 44.9 and 46.8 years, with standard deviations of 10.5 and 13,8 years respectively .

Table (1). Age distribution analysis

	Mean	Mean	t-value	df	p	Valid N	Valid N	Std.Dev.	Std.Dev.	F-ratio	p
	CMJHB	CHB				CMJHB	CHB	CMJHB	CHB		
Age	44.9	46.8	-0.554430	88	0.580691	18	72	10.5	13.8	1.7135	0.213264

3.2. Other demographic profiles of pituitary tumour patients of CMJA and CHB Hospitals

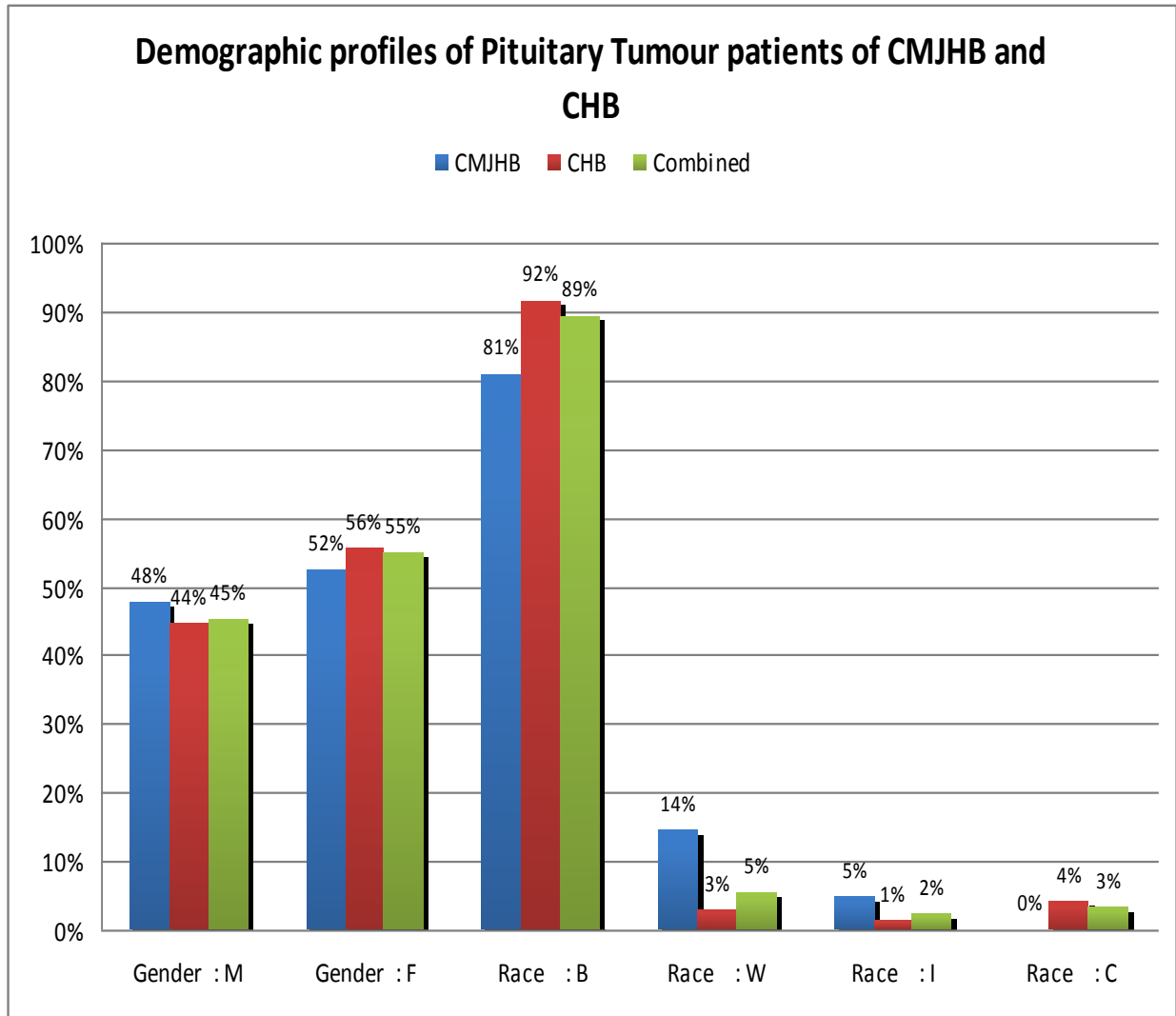


Figure (5). Demographic profiles

The study showed a slight preponderance of females as compared to males. Overall females comprised 55% while males were 45% of the study population. There was no significant difference in the study populations regarding gender from the two hospitals studied.

There is no significant difference between the gender distributions of males and females presenting with pituitary tumours at CMJHB versus CHB: $\chi^2 = 0.00$; $df=1$; $p>0.05$.

With regard to racial distributions, blacks were overall by far the majority of the study population, comprising of 89%, while whites 5%, asians 2% and coloured 3%.

At CMJ Academic Hospital, Blacks were 81% while whites, asians and coloureds comprised 14%, 5% and 0% respectively. CMJ Academic hospital is situated in Parktown, Johannesburg, previously a whites only residential suburb. The hospital serves a wide area which is populated by different races, though blacks still comprise the majority as they are the least likely group to afford private healthcare as the economic imbalance among different races still persists.

The figures at CH Baragwanath Hospital showed an even larger preponderance of blacks at 92% followed by whites at 3%, asians 1% and coloureds at 4%.

CH Baragwanath Hospital is situated in Soweto which is historically a black township according to the segregation rules by the apartheid government and is still almost exclusively populated by blacks. This would explain the overwhelming majority of the black population at CH Baragwanath hospital.

According to the annual estimates from Statistics South Africa, July 2009, blacks comprise 79.3%, whites 9.1%, coloureds 9% and asians 2.6% of the total South African population. Our study population distribution patterns are thus in line with the national demographics with regard to race.

3.3 Clinical presentation

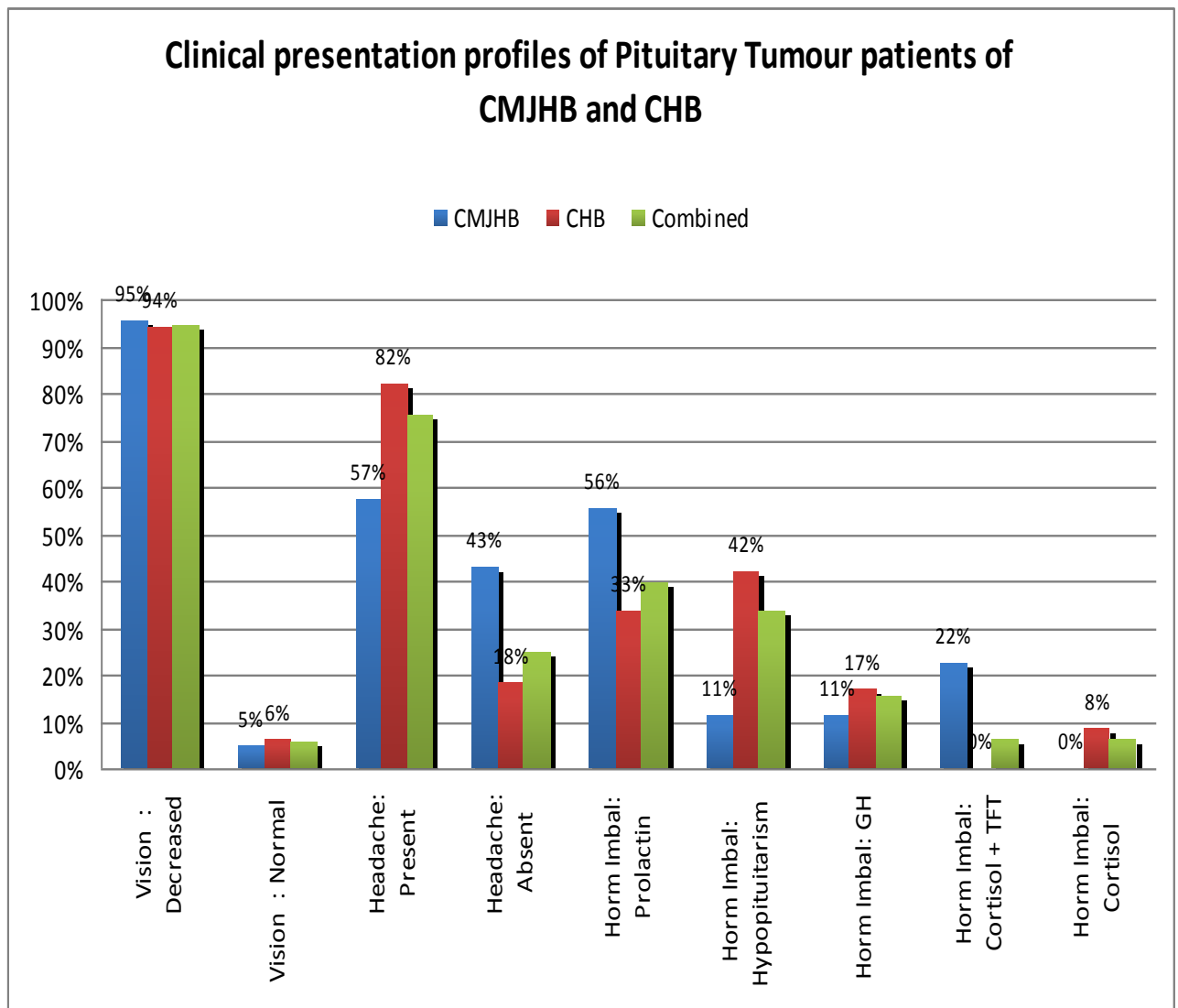


Figure (6). Clinical presentation profiles

With regard to vision, an overwhelming majority presented with various symptoms of visual disturbance, i.e. overall 94,4% had visual disturbance on presentation. There was no statistically significant difference between the CMJ Academic and CH Baragwanath Hospitals patients at 95 and 94% respectively.

Overall 75,3% had headaches as part of the presenting features although CH Baragwanath Hospital patients had a higher prevalence of headaches at 81,7% as opposed to CMJ Academic Hospital patients who only presented with headaches in 57,1% of cases.

Of those who presented with hormonal imbalance, symptoms and signs related to hyperprolactinaemia were the commonest at 39,4%, while hypopituitarism followed at 33,3%, GH at 15,2% and cortisol at 6,1%.

3.4 Imaging

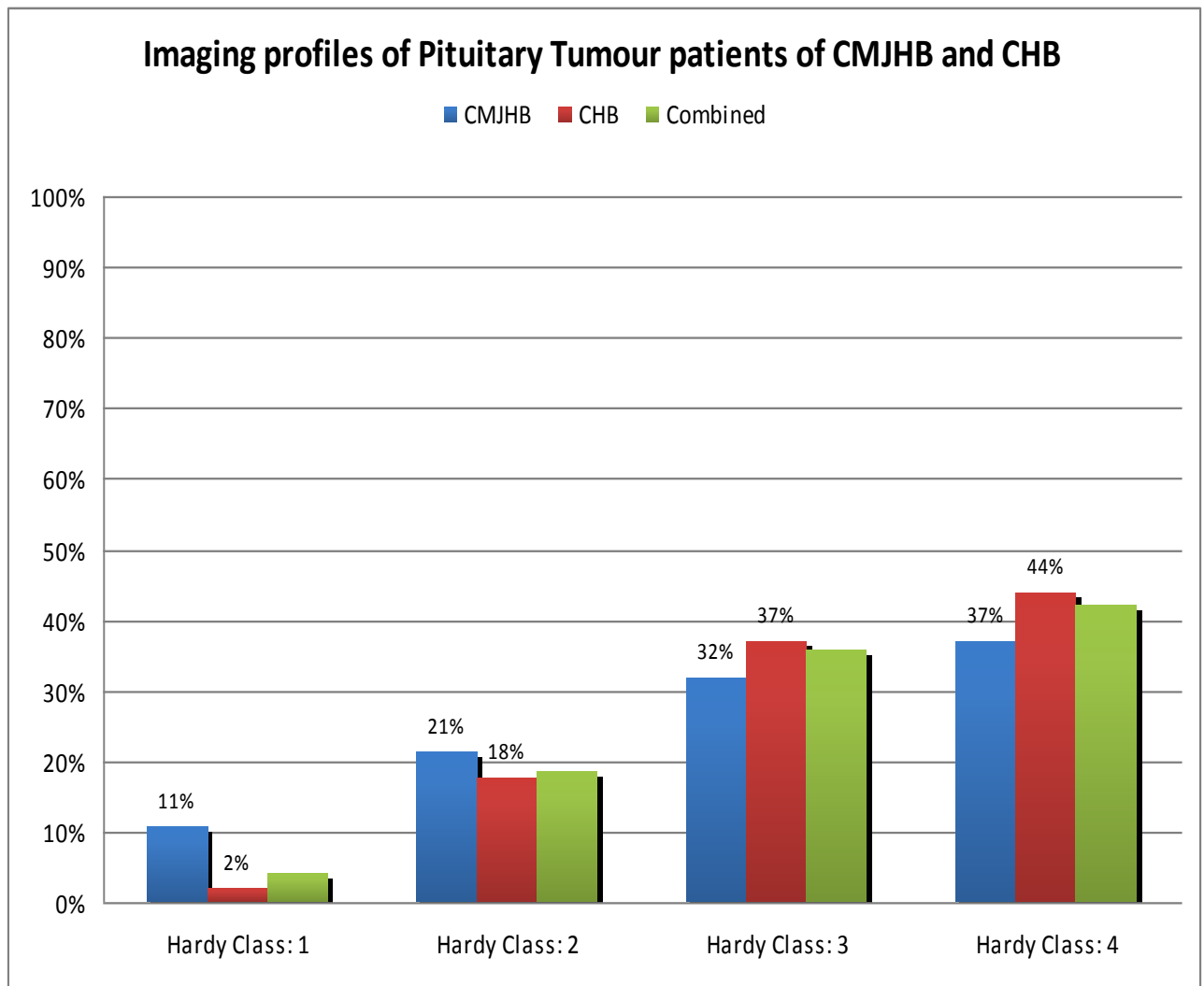


Figure (7). Imaging profiles

According to the profiles above, the commonest tumour size at both our institutions was Class IV according to Hardy classification at 42,1%, followed by Class III at 35,5%, Class II and I at 18,4% and 3,9% respectively.

The results from the two institutions were similar

3.5 Hormonal profiles

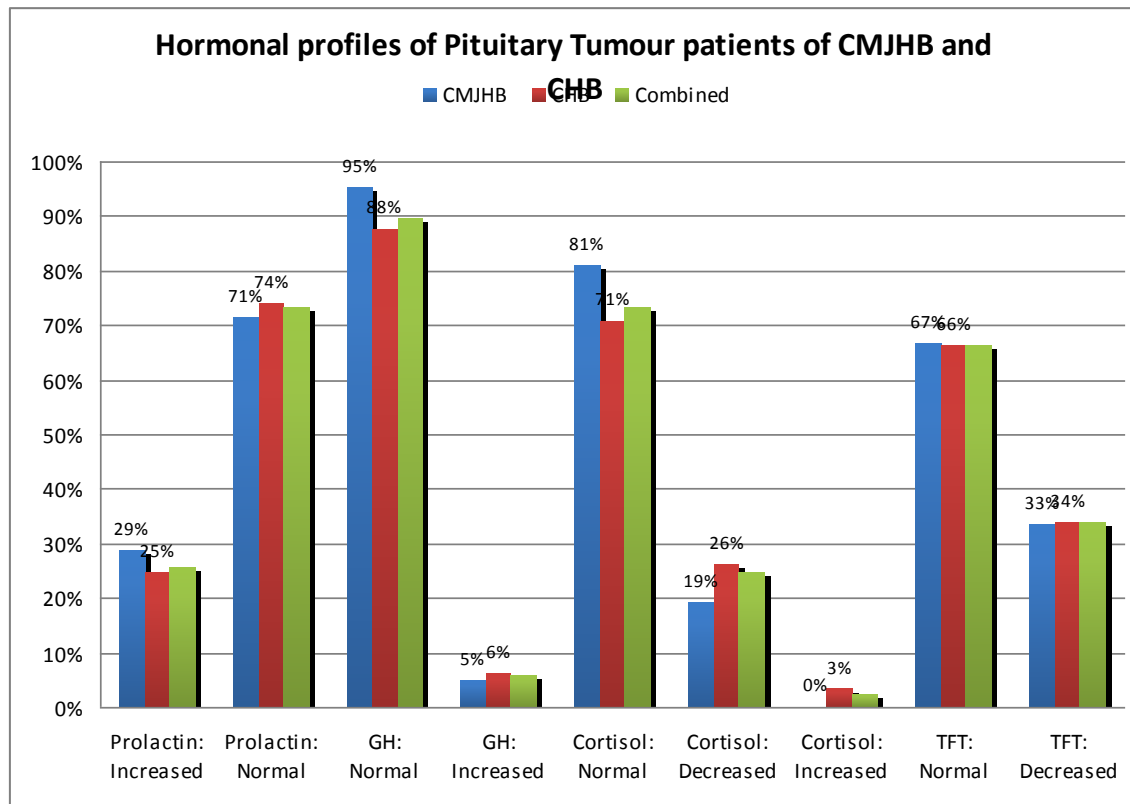


Figure (8). Hormonal profiles.

Overall,

Prolactin was increased in 25,6% of patients, normal in 73,3% and decreased in 1,2%.

GH was normal in 89,5% decreased in 4,7% and increased in 5,8%.

Cortisol levels were normal in 73,3%, decreased in 24,4% and increased in 2,3%. The differences in results from the two institutions were not statistically significant.

66,3% had normal TFT's, while in 33,7% TFT's were decreased. None of the patients studied had increased thyroid hormones.

3.6 Histology

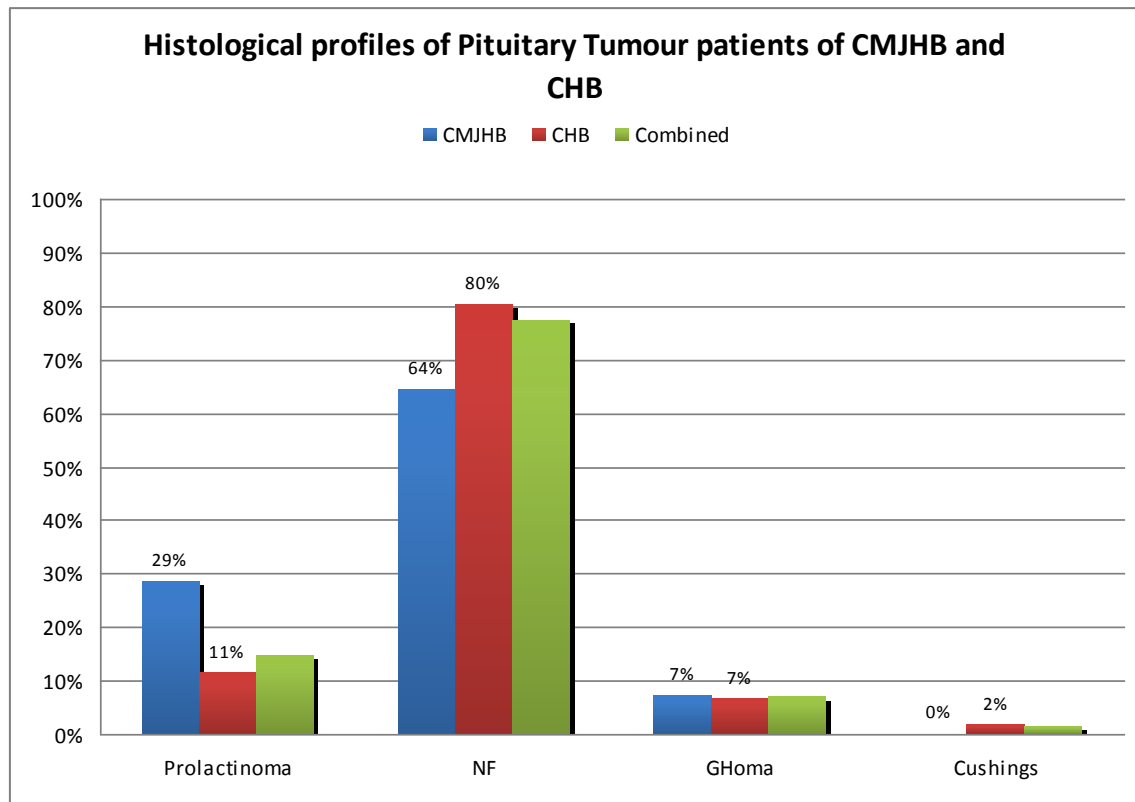


Figure (9). Histological profiles.

Non functioning pituitary adenomas comprised 77,3% of all the tumours analyzed, followed by prolactinomas at an overall 14,7%, acromegaly 6,7% and lastly Cushing's decrease at 1,3%. No thyroid stimulating hormone secreting tumour was encountered.

Prolactinomas were a little more prominent at CMJ Academic Hospital at 28,6% as compared to 11,5% at CH Baragwanath Hospital.

Non functioning tumours were 64,3% at CMJ Academic Hospital as compared to 80,3% at CH Baragwanath Hospital.

3.7 Treatment

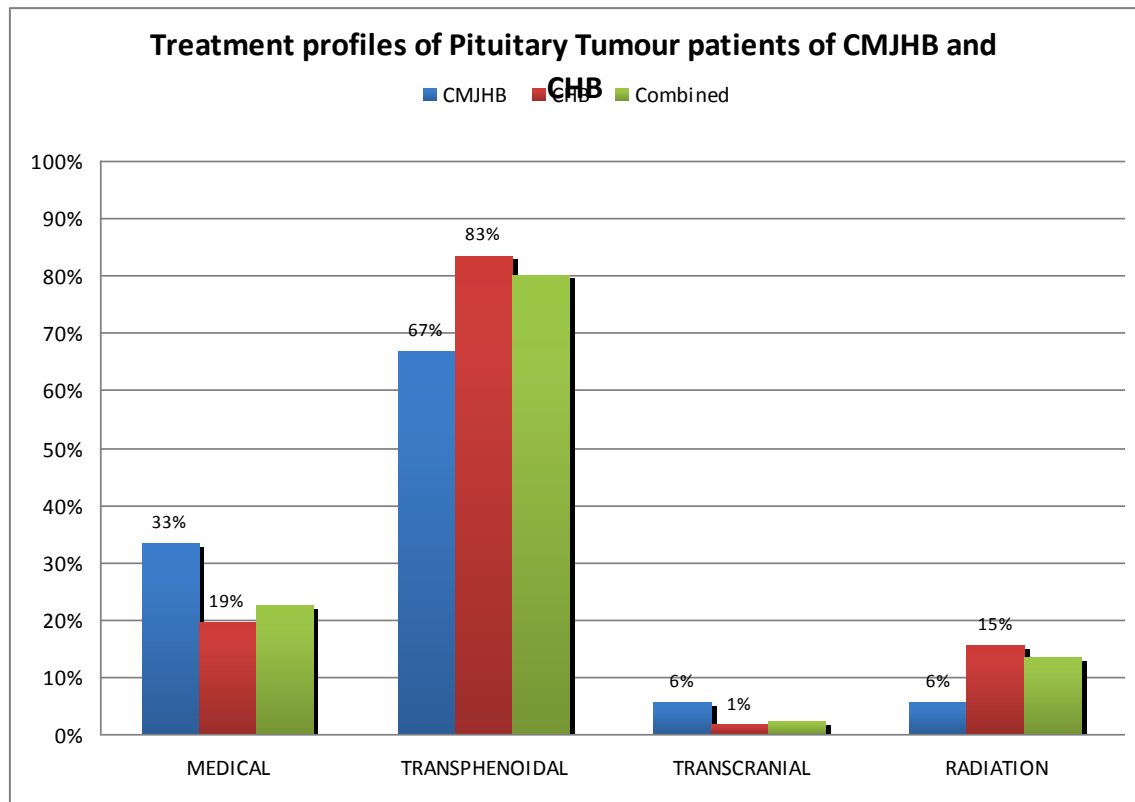


Figure (10). Treatment profiles.

Overall 80% of our patients underwent transphenoidal surgery. Only 2% required transcranial approach as a primary mode of treatment or over and above the transphenoidal approach. 22% underwent medical therapy, mainly for treatment of prolactinomas.

Only 13% had radiation therapy as an adjunctive treatment to transphenoidal surgery for residual tumours.

3.8 Complications

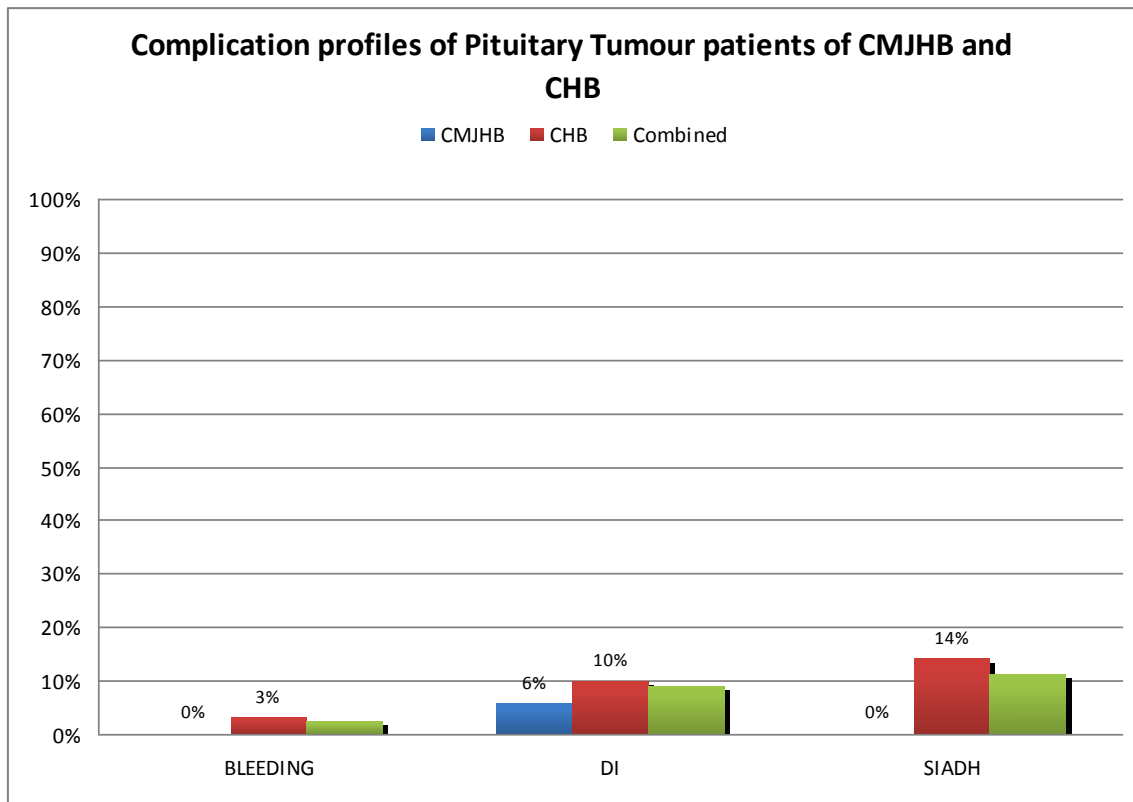


Figure (11). Complication profiles.

Overall 2,2% of patients had post op bleeding while 8,9% had diabetes insipidus and 11,1% had SIADH.

3.9 Outcome

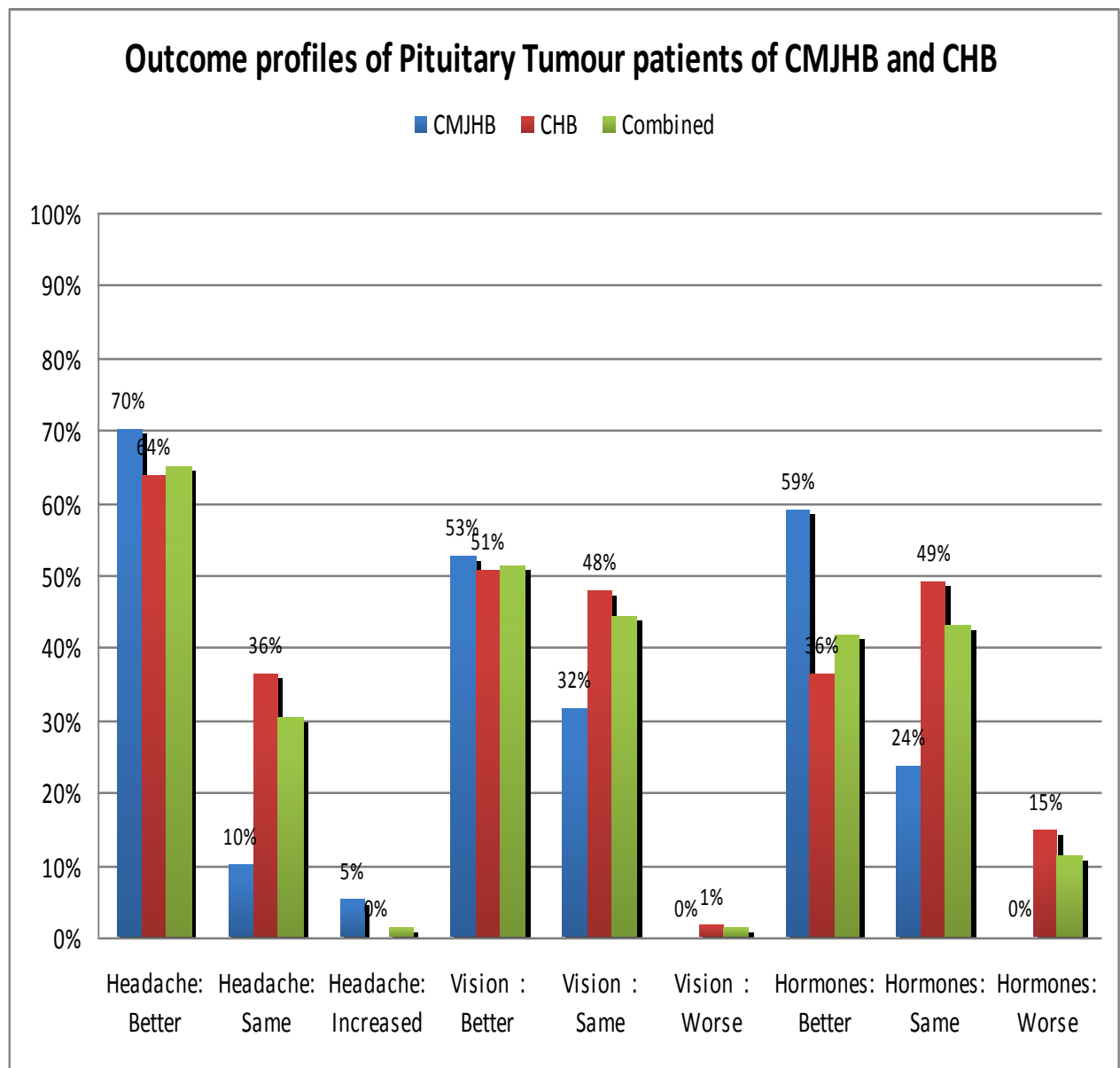


Figure (12). Outcome profiles.

A total of 3 patients refused surgery and one was followed up at the outpatient clinic, while the other two were lost to follow up.

Of the 75,3% who presented with headaches, 65,1% experienced improvement or a cure of their headaches, 30,2% remained the same while 1,2% experienced worsening of headaches post treatment.

In those who presented with visual disturbance, i.e. overall 94, 4% of the total sample, overall 51% had showed improvement, while 44% remained the same. 1% had worsening of vision post treatment.

Hormonal imbalance improved in overall 42%, remained the same in 43%, while 11% got worse, requiring long term hormone replacement.

Table (2). Summary of parameters analysed.

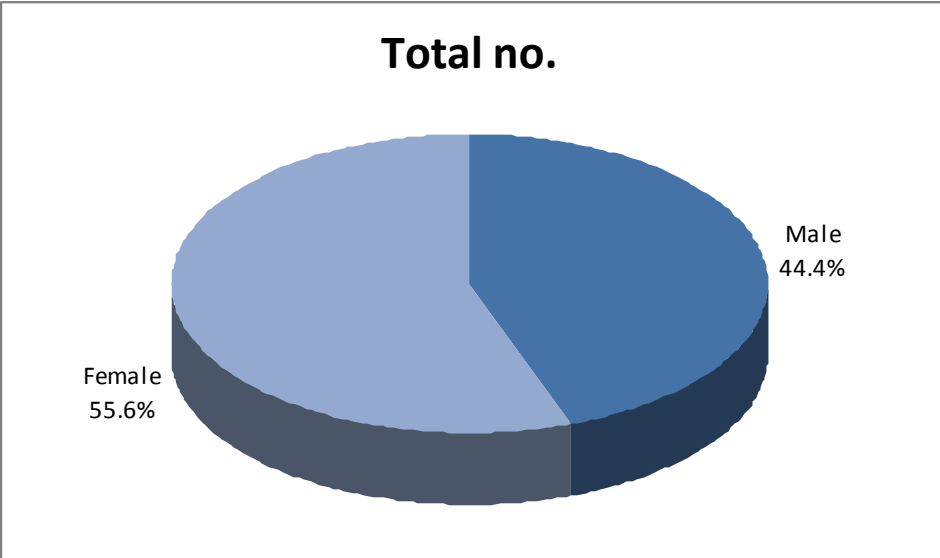
	CMJHB	CHB	Combined	1.00	
Gender : M	47.6%	44.4%	45.2%		
Gender : F	52.4%	55.6%	54.8%	1.00	
Gender : Total	22.6%	77.4%	100.0%		
Race : B	81.0%	91.7%	89.2%	1.00	
Race : W	14.3%	2.8%	5.4%		
Race : I	4.8%	1.4%	2.2%		
Race : C	0.0%	4.2%	3.2%		
Race : Total	22.6%	77.4%	100.0%		
Vision : Decreased	95.2%	94.1%	94.4%	1.00	
Vision : Normal	4.8%	5.9%	5.6%		
Vision : Total	23.6%	76.4%	100.0%		
Headache: Present	57.1%	81.7%	75.3%	1.00	
Headache: Absent	42.9%	18.3%	24.7%		
Headache: Total	25.9%	74.1%	100.0%		
Horm Imbal: Prolactin	55.6%	33.3%	39.4%	1.00	
Horm Imbal: Hypopituitarism	11.1%	41.7%	33.3%		
Horm Imbal: GH	11.1%	16.7%	15.2%		
Horm Imbal: Cortisol + TFT	22.2%	0.0%	6.1%		
Horm Imbal: Cortisol	0.0%	8.3%	6.1%		
Horm Imbal: Total	27.3%	72.7%	100.0%		
Hardy Class: 1	10.5%	1.8%	3.9%		
Hardy Class: 2	21.1%	17.5%	18.4%		
Hardy Class: 3	31.6%	36.8%	35.5%		
Hardy Class: 4	36.8%	43.9%	42.1%	1.00	
Hardy Class: Total	25.0%	75.0%	100.0%		
Prolactin: Increased	28.6%	24.6%	25.6%	1.00	
Prolactin: Normal	71.4%	73.8%	73.3%		
Prolactin: Decr	0.0%	1.5%	1.2%		
Prolactin: Total	24.4%	75.6%	100.0%		
GH: Normal	95.2%	87.7%	89.5%		
GH: Increased	4.8%	6.2%	5.8%	1.00	
GH : Decr	0.0%	6.2%	4.7%		
GH : Total	24.4%	75.6%	100.0%		
Cortisol: Normal	81.0%	70.8%	73.3%		
Cortisol: Decreased	19.0%	26.2%	24.4%	1.00	
Cortisol: Increased	0.0%	3.1%	2.3%		
Cortisol: Total	24.4%	75.6%	100.0%		

TFT: Normal	66.7%	66.2%	66.3%		
TFT: Decreased	33.3%	33.8%	33.7%	1.00	
TFT : Total	24.4%	75.6%	100.0%		
Prolactinoma	28.6%	11.5%	14.7%	1.00	
NF	64.3%	80.3%	77.3%	1.00	
GHoma	7.1%	6.6%	6.7%		
Cushings	0.0%	1.6%	1.3%		
Histology: Total	18.7%	81.3%	100.0%		
MEDICAL : 0	66.7%	80.6%	77.8%		
MEDICAL	33.3%	19.4%	22.2%	1.00	
MEDICAL : Total	20.0%	80.0%	100.0%		
TRANSPHENOIDAL: 0	33.3%	16.7%	20.0%		
TRANSPHENOIDAL	66.7%	83.3%	80.0%	1.00	
TRANSPHENOIDAL: Total	20.0%	80.0%	100.0%		
TRANSCRANIAL: 0	94.4%	98.6%	97.8%		
TRANSCRANIAL	5.6%	1.4%	2.2%	1.00	
TRANSCRANIAL: Total	20.0%	80.0%	100.0%		
RADIATION: 0	94.4%	84.7%	86.7%		
RADIATION	5.6%	15.3%	13.3%		
RADIATION: Total	20.0%	80.0%	100.0%		
BLEEDING: 0	100.0%	97.2%	97.8%		
BLEEDING	0.0%	2.8%	2.2%		
BLEEDING: Total	20.0%	80.0%	100.0%		
DI : 0	94.4%	90.3%	91.1%		
DI	5.6%	9.7%	8.9%		
DI : Total	20.0%	80.0%	100.0%		
SIADH : 0	100.0%	86.1%	88.9%		
SIADH	0.0%	13.9%	11.1%		
SIADH : Total	20.0%	80.0%	100.0%		
Headache: Better	70.0%	63.6%	65.1%	1.00	
Headache: RHT	15.0%	0.0%	3.5%		
Headache: Same	10.0%	36.4%	30.2%		
Headache: Increased	5.0%	0.0%	1.2%		
Headache: Total	23.3%	76.7%	100.0%		
Vision : Better	52.6%	50.7%	51.1%	1.00	
Vision : Same	31.6%	47.8%	44.3%		
Vision : RHT	15.8%	0.0%	3.4%		
Vision : Worse	0.0%	1.4%	1.1%		
Vision : Total	21.6%	78.4%	100.0%		
Hormones: Better	58.8%	36.4%	41.7%	1.00	
Hormones: Same	23.5%	49.1%	43.1%		

Hormones: RHT	17.6%	0.0%	4.2%		
Hormones: Worse	0.0%	14.5%	11.1%		
Hormones: Total	23.6%	76.4%	100.0%		

Table (3). Chi-squares analysis

Gender	Chi-square: 5.31250,	df=2,	p=.070216
Race	Chi-square: 7.18750,	df=3,	p=.066162
Vision	Chi-square: .002776,	df=1,	p=.957983
Headache present	Chi-square: 1.82777,	df=1,	p=.176394
Hormonal imbal	Chi-square: 8.87051,	df=4,	p=.064427
Hardy	Chi-square: 4.00527,	df=3,	p=.260902
Prolactin	Chi-square: .781632,	df=2,	p=.676506
GH	Chi-square: 1.18815,	df=2,	p=.552074
Cortisol	Chi-square: .735751,	df=2,	p=.692204
TFT	Chi-square: .157690,	df=1,	p=.691293
Histology	Chi-square: 2.88340,	df=3,	p=.409959
Medical	Chi-square: 1.60714,	df=1,	p=.204897
Transphen	Chi-square: 2.50000,	df=1,	p=.113849
Transcranial	Chi-square: 1.15057,	df=1,	p=.283433
Radiation	Chi-square: 1.17788,	df=1,	p=.277790
Bleeding	Chi-square: .511364,	df=1,	p=.474551
DI	Chi-square: .308689,	df=1,	p=.578487
SIADH	Chi-square: 2.81250,	df=1,	p=.093536
Headaches	Chi-square: 2.15761,	df=1,	p=.141869
Vision better	Chi-square: .722876,	df=1,	p=.395204
Hormones better	Chi-square: 5.58342,	df=1,	p=.018133



Gender	Total no.	Percent
Male	40	44%
Female	50	56%

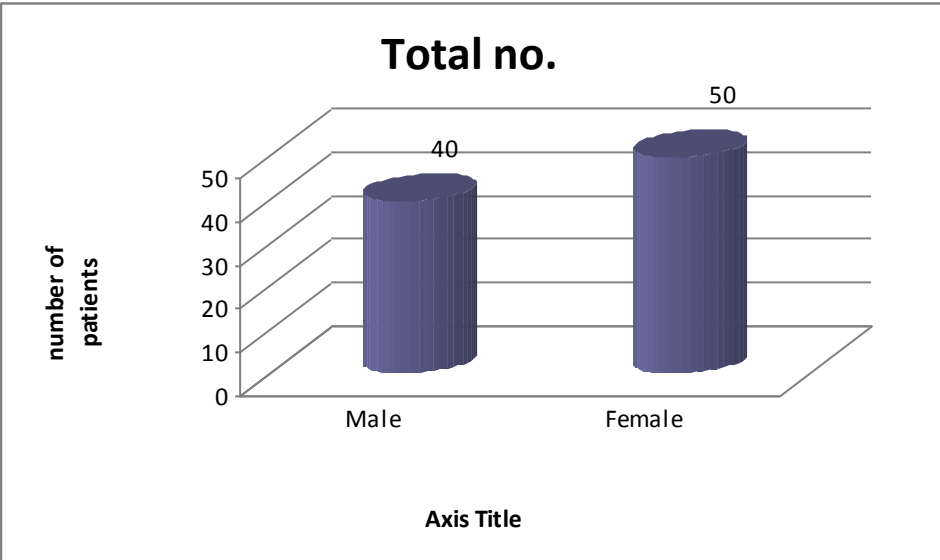


Figure (13). Age distribution

Table (4). Comparison of age distribution with other studies

obs					exp				diff		
	Male	Female			Male	Female			Male	Female	Chi square
KM	40	50	90	KM	39.05941	50.94059	KM	KM	0.022651	0.017368	0.0469981
Lit	223	293	516	Lit	223.9406	292.0594	Lit	Lit	0.003951	0.003029	
	263	343	606								
	obs				exp				diff		
	Male	Female			Male	Female			Male	Female	Chi square
CMJHB	8	10	18	CMJHB	8	10	KM	CMJHB	0	0	0
CHB	32	40	72	CHB	32	40	Lit	CHB	0	0	
	40	50	90								

4. DISCUSSION

Pituitary tumours are not uncommon, comprising 10-15% of primary brain tumours^(1,2,3), with around 25% detected incidentally⁽¹⁾. Peak incidence occurs between the third and six decade. In our study of ninety three 93 patients, the overall average age was 46,7 years, ranging from age seventeen to seventy nine years. Our results were thus in agreement with the above publications.

The gender distribution of our study population showed a marginal preponderance of females (51), 56% and 42 males (42) 44%. These figures are in agreement with those published in the literature, as they are widely reported as occurring more frequently in women of child bearing age, yet evenly distributed in autopsy series⁽¹⁾. Indeed the changes in menstrual cycle, along with infertility appear to play a role in the higher numbers of females.

An overwhelming majority (94%) of our patients presented with some form of visual disturbance. These included unilateral or bilateral decrease in visual acuity, ranging from mild decrease to complete blindness, various forms and degrees of visual field defects. Others included extraocular cranial nerve palsies.

Formal visual field and acuity tests were performed by the ophthalmologists to assess pre and post treatment level of visual disturbance. A common and disturbing issue noted was the fact that our patients tended to present very late, often with a history of more than two years of progressively worsening visual acuity. Some of the underlying reasons include patient apathy, social acceptance of visual deterioration as part of the ageing process, lack of resources, especially with patients from rural areas, thus making it difficult to access basic health care facilities and inaccurate diagnosis and late referrals by primary healthcare practitioners to tertiary centers. An aggressive community education campaign possibly in conjunction with ophthalmologists, optometrists, appropriate government departments and primary healthcare practitioners appears mandatory in order to raise awareness regarding visual problems. Hopefully that will improve the time of referral and thus increase the rate of visual preservation with an early and appropriate treatment.

Indeed a significant number of our pituitary tumour referrals are from our ophthalmology department, having been through optometrists and general practitioners.

The second most common presentation was headaches (75%). These varied from raised intracranial pressure type headaches to those localized subjectively behind the eyes. These could be attributed to the mass effect and invasion or involvement of pain sensitive structures such as the dura and blood vessels.

Our figures for those who presented with headaches and visual disturbance appear significantly higher than those published in other studies quoted earlier⁽⁷⁾. The underlying reasons have also been mentioned above.

The presenting symptoms and signs attributable to hormonal imbalance were divided into two categories namely, clinical features of hypopituitarism and those of individual hormone hyper secretion.

Overall 33% presented with features of hypopituitarism, mainly decreased cortisol and thyroxin as confirmed by laboratory testing.

Of the hyper secretion syndromes, those attributable to prolactin were the commonest. Of those who presented with clinical features of hormonal disturbance, 39% had features of hyperprolactinaemia, although true prolactinomas only made 14.7% of our total study population. Galactorrhoea, menstrual irregularities and infertility were common among women while impotence and loss of libido were reported more in males. Surprisingly only a few males volunteered the information relating to their associated sexual dysfunction. Many appeared embarrassed and indeed reluctant to admit or discuss their sexual problems. This may underlie a cultural taboo with regard to discussing sexual matters in the communities served by our teaching institutions.

Patients presenting with acromegaly and gigantism made up 6.7% of our study population. In this case our results differ with the 22% quoted elsewhere⁽³⁾. Their (acromegalics) ages of presentation ranged from 23 to 56 years with a mean of 36,2 years.

Cushing's disease was encountered fairly infrequently in our study population averaging only 6% of the total number of patients studied. They presented mainly with disfiguring effects of hypercortisolaemia including truncal obesity, hirsutism and alopecia. Other features included poorly controlled systemic hypertension, fatiguability and muscle weakness, hyperglycaemia and hypokalaemia. Radiologically, they commonly presented as micro adenomas.

This early presentation is due to the profound physical effects of hypercortisolaemia mentioned above.

We used MRI of the brain and computed tomography where MRI was not available or feasible. CT pictures included axial and coronal views of the sellar. Over and above that, MR angiography was also employed to demonstrate the vascular structures in the circle of Willis. Only rarely digital subtraction angiography was necessary to elucidate the involvement of vascular structures mentioned. The radiological features were classified according to the Hardy grading classification. Due to the late presentation of our patients alluded to earlier, it was not surprising to note that the majority of our patients presented with Hardy class 4 (42%), class 3 (36%), class 2 (18%) and class 1 (4%). Class 1 comprised mainly those who presented with Cushing's disease as previously mentioned. 80% of our patients were treated with transphenoidal surgery. Only 2% required additional transcranial approach for tumours extending into the anterior and middle fossae, beyond the reach of the transphenoidal approach. Those with residual tumours were then subjected to radiation therapy. Prolactinomas were treated medically with bromocryptine or cabergoline.

The complications documented were unexpectedly low, with Syndrome of inappropriate Anti Diuretic Hormone secretion (SIADH) the commonest at 15,6% of those who underwent TSS. This was mainly transient and resolved within a week of treatment with fluid restriction.

Diabetes Insipidus (DI) was the second most common complication at 12,5% of those who had transphenoidal surgery. This was usually transient and successfully controlled with desmopressin (DDAVP).

Post operative bleeding and CSF leak were rare at 2%. Outcome was very favourable with 65% of the patients reporting a complete cure or significant

reduction in their headaches after treatment. These headaches are probably on the basis of tumour invasion or compression of pain sensitive structures such as dura and blood vessels.

Improvement in visual disturbance, mainly visual acuity and field defects was less dramatic yet significant nevertheless. Overall 51% had an improvement in vision post treatment while 44% remained the same and 1% reported worsening of vision. CT scans are readily available to the referring hospitals, thus have no impact in the time to diagnosis.

42% of patients with hormonal imbalance showed improvement or normalization of hormone levels following treatment. This included 100% of the prolactinomas, the rest made up of those who presented with hypopituitarism. This illustrates the effectiveness of dopamine agonists in reduction of the raised level of serum prolactin. However 11% had worsening of hormone levels post operatively while 43% remained the same, necessitating long term hormone replacement in the form of prednisone and eltroxin.

5. CONCLUSION

The demographic profiles of patients presenting to CMJ Academic and CH Baragwanath Hospitals are similar to those published in the literature from other institutions. There is a slight female preponderance with a mean age of 46 years.

Clinical presentation involves visual disturbances in the overwhelming majority of patients, along with headaches and features of hormonal imbalance.

Majority (99%) of non functioning tumours are treated with transphenoidal surgery while prolactinomas are usually treated with dopamine agonists with favourable outcome in vision, headaches and hormone imbalance.

There has been no statistically significant difference in the data from the two teaching hospitals studied.

Our patients tend to present late with large expansive tumours and irreversible visual disturbances. Educational measures need to be put in place to correct the matter. The community, primary health care and optometrists must be mobilized to be on high alert regarding loss or deterioration in visual acute.

Secondly, very few of our patients i.e. 13% received post operative radiation therapy even though the majority i.e. 42% presented with Hardy 4 suggesting poor likelihood of complete resection. Thus a concerted effort must be put in place with regard to follow up treatment.

Lastly, our record keeping needs to be improved. The details of the admission notes, management during and after hospital admission need to be documented meticulously. Poor record keeping was the major limitation to the study leading to difficulties assessing some of the parameters studied.

REFERENCES

1. Kamal Thapar, Edward R Laws. Pituitary Tumours: Functioning and non-functioning, Youmans Neurological Surgery 2004; ch 66: 1170; Elsevier Philadelphia.
2. Jason A Jarzembowski, Paul E McKeever. The pathologic perspective on the pituitary. Review of Endocrinology: March 2008, 30-35. Radiation Oncology Biol. Phys. 1279-1286.
3. Oruckaptan HN, Senmersim O, Ozcan OE, *et al.* Pituitary adenomas: Result of 684 surgically treated patients and review of literature; Surg Neurol 2000 Mar; 53(3):211-9.
4. Milker-Zabel S, Debus J, Thilmann C *et al.* Fractionated stereotactically guided radiotherapy and radiosurgery in the treatment of functional and non-functional adenomas of the pituitary gland. Int.J. Radiation Oncology Biol. Phys., Vol 50, No.5, 2001, 1279-1286.
5. Gsponer J, De Tribolet N, Deruaz JP *et al.* Diagnoses, treatment and outcome of pituitary tumours and other abnormal intrasellar masses: Medicine (Baltimore) 1999 Jul 78(4):236-69.
6. Mulinda JR. Pituitary macroadenomas: eMedicine; Nov 2, 2007.
7. Shamin MS, Bari ME, Kursheed F *et al.* Pituitary adenomas: Presentations and outcomes in a South Asian Country, CAN J. Neurol Sci. 2008 May; 35(2):198-203.
8. Verrees M, Arafah BM, Selman WR. Pituitary tumour apoplexy: characteristics, treatment and outcomes. Neurosurgery focus, 2004 Apr 15; 16(4): E6.
9. Cho WJ, Joo SP, Kim TS *et al.* Pituitary apoplexy presenting as isolated third cranial nerve palsy with ptosis: two case reports. J Korean Neurosurg Soc, 2009 Feb; 45(2): 118-21.
10. Sharma JB, Roy KK, Mohanraj P *et al.* Pregnancy outcome in pituitary tumours: Arch Gynecol Obstet, 2009 Sept; 280(3):401-4.

11. McMorran J, Crowther DC, McMorran S *et al*. Pituitary adenomas: General Practice Notebook; UK medical reference on the worldwide web. <http://www.gpnotebook.co.uk>.
12. Thamburaj VA. Pituitary adenomas: Thamburaj.com; neurosurgery on the web. <http://www.thamburaj.com>
13. Chanson P, Salanare S. Diagnosis and treatment of pituitary adenomas: Minerva Endocrinol. 2004 Dec; 29(4): 241-75.
14. Post KD, Shrivastava RK. Functioning pituitary tumours: Principles of Neurosurgery 2005, ch 38: pg 608-620; Elsevier-Mosby, Philadelphia.
15. Devin JK, Blevins LS. Endocrinologic approach to the evaluation and management of the patient undergoing surgery for a pituitary tumour: Operative Neurosurgical techniques, 2006 Ch 24; 300. Saunders Elsevier, Philadelphia PA.
16. Bonneville JF, Cattin F, Bonneville F. Imaging of pituitary adenomas: Presse Med. 2009 Jan;38(1):84-91.
17. Greenberg MS. Pituitary adenomas: Handbook of Neurosurgery 2001, Ch 14: 419-436. Thieme; New York, NY.
18. Buchfelder M. Management of aggressive pituitary adenomas: Current treatment strategies: Pituitary 2009;12(3);256-60.
19. Ali R, Noma U, Jansen M *et al*. Ectopic pituitary adenoma presenting as midline nasopharyngeal mass: Ir J. Med Sci 2009 Jan 8. [E pub ahead of print].
20. So G, Takeshita T, Morofuji Y *et al*. Non functioning suprasellar ectopic pituitary adenoma: No Shinkel Geka; 2008 Dec, 36(12): 1121-5.
21. D'Ambrosio AL, Syed ON, Grobelny BT *et al*. Simultaneous above and below approach to giant pituitary adenomas: Surgical Strategies and long term follow-up. Pituitary 2009 12(3):217-25.
22. Fleseriu M, Yedinak C, Campbell C *et al*. Significant headache improvement after transphenoidal surgery in patients with small lesions: J Neurosurg 2009;Feb;110(2):354-8.

23. Gnanalingham KK, Bhattacharjee S, Pennington R *et al.* The time course of visual field recovery following transphenoidal surgery for pituitary adenomas: J. Neurol Neurosurg Psychiatry 2005; 76(3): 415-9.
24. Wei T, Zuyuan R, Changbao S *et al.* Hyponatraemia after transphenoidal surgery of pituitary adenoma: Chin Med Sci J 2003 Jun; 18(2): 120-3.
25. Crowley RW, Dumont AS, Jane JA jnr. Bilateral intracarvenous carotid artery pseudoaneurysms as a result of sellar reconstruction during transphenoidal resection of a pituitary macroadenoma: Case report; Minimum Invasive Neurosurgery 2009 Feb, 52(1): 44-8.
26. Menon G, Bahuleyan B, Nair S. Acute subdural haematoma after transphenoidal surgery: J Clin Neurosci 2009 Jan; 16(1): 160-2 [E pub 2008 Nov 14]
27. Fusco A, Lugli F, Sacco E *et al.* Efficacy of the combined carbegolin and octreotide treatment in a case of a dopamine agonist resistant macroprolactinoma: Pituitary 2009 Jan 17; [E pub ahead of print].
28. Ferone D, Pivonello R, Lastoria S *et al.* In vivo and in vitro effects of octreotide, quinagolide and carbegolin in four hyperprolactinaemic acromegalics. Correlation of somatostatin and dopamine D2 receptor scintigraphy: Clin Endocrinol (Oxf) 2001 Apr; 54(4): 469-77.
29. Yang SH, Lee KS, Lee KY *et al.* Pituitary apoplexy producing internal carotid artery compression: a case report. J Korean Med Sci.2008 Dec;23(6):1113-7.