PITUITARY ADENOMA: RETROSPECTIVE STUDY AND ANALYSIS OF FACTORS THAT AFFECT THE OUTCOME OF SURGICAL TREATMENT

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Abstract

Background: Pituitary adenomas are benign epithelial tumors, representing about 10% of intracranial tumors. They present as visual or hormonal disturbances or both. Attention to details in the treatment of theses benign tumors can't be overemphasized in order to achieve best results.

Objective: The aim of this work is to review the clinical and radiological features of these relatively common tumors, and identify factors that affect the outcome of surgical treatment and recurrence.

Methods: This study was carried out retrospectively by reviewing the medical records of all patients with pituitary adenomas treated in the period of four years, and collecting clinical, radiological, laboratory, and surgical data. Follow up of 1-4 years was obtained on all patients.

Results: There were 55 patients (31 male and 24 female) the median age was 37 year. The main presenting symptoms were visual deterioration in 49%, symptoms of endocrine disturbance in 35.3%, headache in14.5%, behavioural changes in 1.8% and seizure in 1.8%. The most common hormonal disturbance was hyperprolactinemia (32.7%). Lateral skull x-ray showed grade III sellar enlargement with erosion of the dorsum sellae in 87.2%. Brain CT scan showed isodense mass in 76% of cases, with suprasellar extension in 82.6% and contrast enhancement in 85.7%. The operative approaches were right subfrontal craniotomy in 83.6% and tarns-sphenoidal (sub labial) approach in 16.3%. Intracapsular (subtotal) removal was achieved in 70.9%, while capsular (total) removal was achieved in 29.1%. Tumour recurred in 3 patients; two of them had postoperative radiotherapy and all had originally aggressive tumors.. There were 2 cases of post radiation glioma.

Conclusion: The results of the study were similar to those published. Pituitary adenoma is usually benign relatively avascular soft in consistency with characteristic clinical and radiological features. Unless associated with advanced optic atrophy with visual loss there is dramatic improvement of optic nerve function following surgery. Transient diabetes insipidus is the commonest postoperative complication mainly following trans-sphenoidal approach. The only factor that enhances recurrence is tumour aggressiveness. Postoperative radiotherapy is only indicated for aggressive invasive pituitary adenoma.

Key words: Pituitary, Adenoma, Outcome.

IRAQI J MED SCI, 2005; VOL. 4 (2): 197-209

Introduction

Pituitary adenomas are common benign epithelial neoplasms that are composed of and derived from adenohypophysial cells. They represent about 10% of intracranial tumors[1]. In most cases they are histologically benign, slow growing small neoplasms confined to the sella tursica. Some however grow faster, invading surrounding tissues, and cause local symptoms such as visual disturbances, headache, and compression of non tumorous pituitary tissue, resulting in varying degrees of hypopituitarism[2].

Pituitary adenomas can be classified according to their size, radiolographic appearance, endocrine function, morphology, and cytogenesis. Neurosurgeons frequently classify pituitary adenoma on the basis of size

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Received 30th November 2003: Accepted 21st December 2005

and invasiveness, as determined by imaging studies (MRI, CT scan and X-ray films of the skull), with respect to the size, microadenomas are smaller than 1cm in greatest diameter, and macroadenomas are larger than this[1].

Microscopically pituitary adenomas are generally monomorphous proliferation, consists of a single relatively uniform, homogenous staining cell population with no acinar arrangement, surrounded by a condensed rim of non tumorous pituitary tissue and its condensed reticuline network, which collectively constitute the adenomas pseudocapsule. Pituitary adenomas can be classified into acidophilic, basophilic, and cromophobe adenomas according to their staining property with hematoxylin-eosin preparation[1].

Pituitary adenomas present either as hormonal dysfunction, or as visual disturbance due to chiasmal compression. The management of pituitary adenoma is challenging, as complete surgical removal is sometimes difficult to achieve and is usually associated with substantial morbidity and mortality, on the other hand, other therapeutic modalities such as radiosurgery and radiotherapy are of limited efficacy on their own, and are used as adjuvant to surgical treatment[3-6].

Methods

The material of this study included 55 consecutive patients with pituitary adenoma surgically treated during the period of January1997 to April 1999 in four neurosurgical centers in Baghdad, Al-Kadmya hospital (T), the neurosurgical hospital, the neurosurgical dep. Medical City (T) and the Nursing home, Medical City. The patient's files were reviewed and all biographic, clinical, radiological, and treatment data uniformly collected according to previously designed data sheet. The collected data included: patients age (according to decades), sex, duration of illness and the presenting symptom.

The physical signs documented include visual acuity and visual fields, presence of optic atrophy on fundus examination, evidence of endocrine dysfunction as acromegaly, hyperprolactinemia and the development of secondary sexual characteristics. Serum hormonal level (prolactin, growth hormone, thyroxine, cortisol, follicular stimulating hormone (FSH) and leutenizing hormone (LH) was recorded. On lateral skull X-ray the findings were classified into grades as follow[7].

G_I: Normal size sella with focal erosion

G_{II}: Enlarged not eroded sella

G_{III}: Enlarged eroded, ballooned or double floor sella

G_{IV}: Completely destructed sella (Ghost sella)

On CT scan, MRI and MRA data such as extension of the tumor to the frontal, and temporal lobes and to the cavernous sinus as well as hydrocephalus was recorded.

Operative data were documented including the surgical approach (right sub frontal craniotomy or sub labial trans-sphenoidal approach). The choice of surgical approach depended on the presence or absence of extrasellar extension of the tumor. The extent of tumor excision whether total (capsular) or subtotal (intracapsular) resection, Outcome including complications, mortality, and Postoperative radiotherapy was recorded.

Follow-up notes were reviewed and the patient's clinical, endocrinological and radiological findings were documented. Tumor recurrence was defined as re-growth of tumor as appeared in the follow up CT scan and MRI or both, or recurrence of symptoms. The outcome of treatment was considered good if the patient is alive, having improved or stable useful vision, good school performance or is employed and poor

outcome if the patient condition did not fulfill one or more of the above criteria or is dead.

Results

The study included 55 patients (31 males and 24 females) the median age was 36 years. Figure I summarize the age and gender distribution. Most of the patients were in the forth decade. There is female preponderance in the 2nd and 3rd decades, male incidence increased in the 4th and 5th decades.

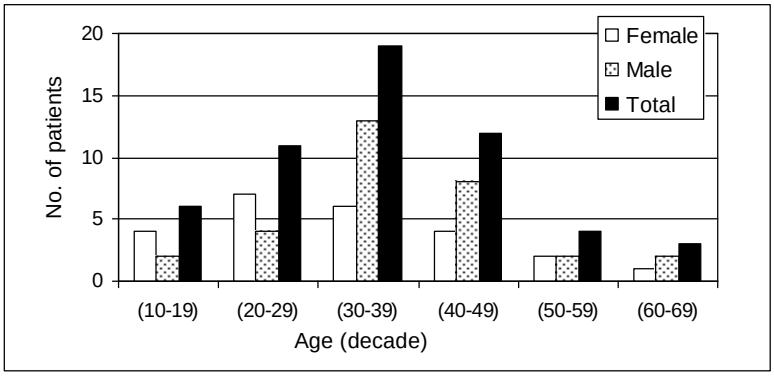

Figure 1: Age and Gender

Visual disturbance in the form of blurring of vision was the commonest presenting symptom (45.4%) followed by amenorrhea 18% and acromegalic feature 16.3% (Table 1). The one patient presented with diplopia as the first complain was diagnosed later to have had pituitary apoplexy.

Table 1: The presenting symptoms of pituitary adenomas

Symptom	No.	Percent
Visual disturbance (decreased visual acuity and field defect)	25	45.4
Headache (non specific)	8	14.5
Diplopia	1	1.8
Loss of vision	1	1.8
Impotence and loss of libido	1	1.8
Amenorrhea	10	18
Acromegalic features	9	16.3

Hyperprolactinemia, proved by hormonal assay, presenting as loss of libido and impotence in males and amerorrhea-galactarrhea in females was present in the majority of patients 72%, followed by excessive growth hormone secretion presenting as acromegaly or gigantism in 64% of cases (Table 2).

Table 2: Hormonal disturbances associated with Pituitary adenoma (25 patients).

Type of hormonal disturbance	No.	Percent	Female	Male	Percent
Acromegaly and gigantism	16	64	6	10	29
Hyperprolactinemia	18	72	6	12	32.7
Cushing's disease	1	4	1	-	1.8
Hypogonadism	1	4	-	1	1.8

Headache was the commonest symptom (90.9%). Progressive visual deterioration coming next in frequency (78%0, all of them had decreased visual acuity and 63.3% of patients had visual field defect usually in the form bitemporal hemianopia. Unilateral visual loss was detected in 27%, and primary optic atrophy was observed in 29% of patients. Papilledema was seen in four patients (7.2%) two of them had hydrocephalus. Diplopia was complained of in 4 patients (7.2%) three patients had pure sixth cranial nerve palsy and one patient had complete left sided ophthalmoplegia (Tables 3 and 4).

Table 3: Symptoms due to pressure effect of pituitary adenoma (55 patients)

Symptoms	No.	Percent
Headache	50	90.9
Visual field defect	43	78
Diplopia	4	7.2
Unilateral loss of vision	15	27.2
Behavioural changes	1	1.8
Seizure	1	1.8
Pituitary apoplexy	1	1.8

Table 4: Signs of space-occupying effect in relation to the total number of patients with pituitary adenomas

Signs	No.	Percent
Decreased visual acuity	43	78.1
Visual field defect (temporal hemianopia)	35	63.3
Primary optic atrophy	16	29
Papilledema	4	7.2
Ocular nerve palsy	4	7.2
Trigeminal nerve affection	1	1.8

On skull X-ray the majority of patients had sellar enlargement (94.5%), while normal size sella found in only (5.4%). Grade III sellar enlargement was the commonest finding (87.2%), (Table 5).

Table 5: Skull X-ray findings in patients with pituitary adenomas (55 patients)

Appearance	Grade	No.	Percent
Normal sella with focal erosion	I	3	5.4
Intrasellar calcification	-	1	1.8
Enlarged sella turcica	II → IV	52	94.5
Enlarged not eroded sella	II	1	1.8
Enlarged eroded sella	III	30	54.5
Enlarged double floor sella	III	3	5.4
Ballooned sella	III	15	27.2
Completely destructed sella (Ghost sella)	IV	3	5.4

Pituitary adenomas were isodense in the majority of patients (76%). Supra sellar extension was the commonest finding (82.6%), while no tumor extension was detected in 17.3%. - Hydrocephalus was seen in only two patients (4.3%). In contrast, in a study, which was performed in 35 patients, 85.7% had enhancing adenoma (Table 6).

Table 6: C.T. Finding in patients with pituitary adenomas (46 patients)

Finding	No.	Percent
CT without contrast		
1- Density	35	76%
- isodense	3	6.5%
- hypo dense	8	17.3%
- hyper dense		
2- Extension		
- suprasellar	38	82.6%
- lateral	13	28.2%
- anterior	1	2.1%
- no extension	8	17.3%
3- Ventricular dilatation (Hydrocephalus)	2	4.3%
CT with contrast (35 patients)		
1- Enhanced	30/35	85.7%
2- Not enhanced	5/35	14.3%

MRI and MRA were the most useful imaging modalities in evaluation they were performed in nine patients (Figures 2 and 3).

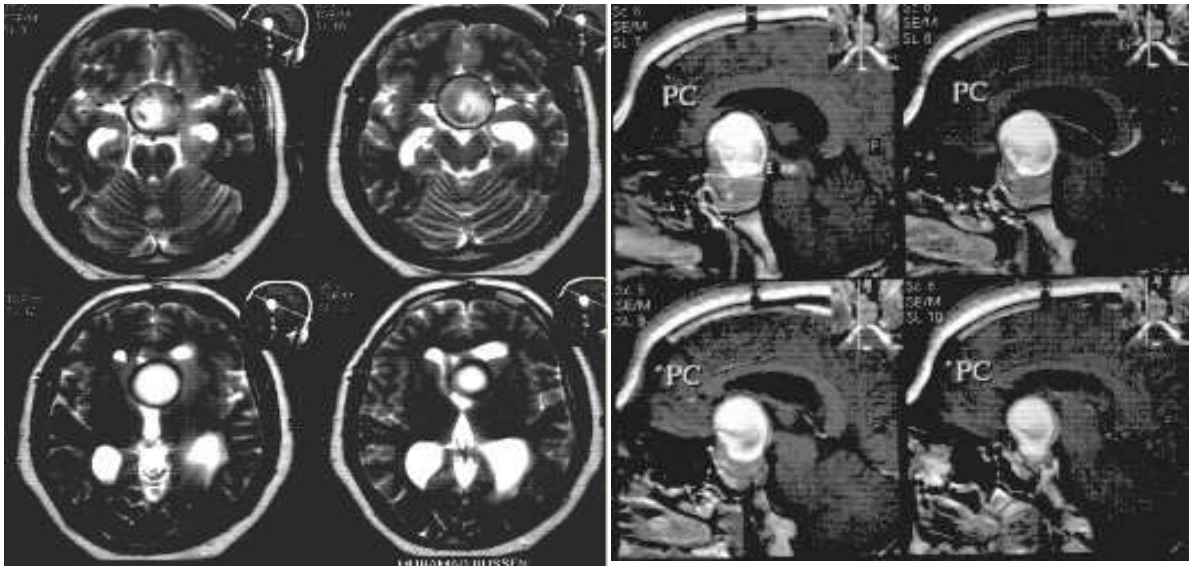

Figure 2: Pituitary adenoma, with suprasellar extention (MRI, Axial and sagital sections)

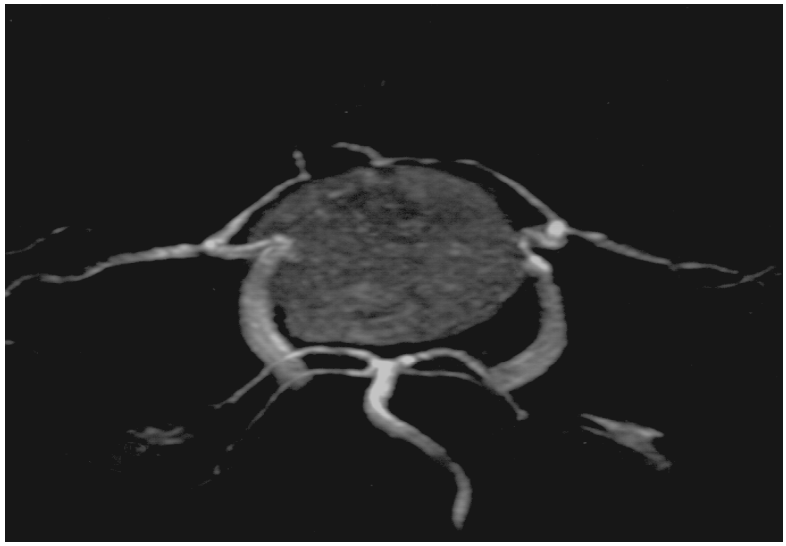

Figure 3: Pituitary adenoma (MRA)

Most of the adenomas were soft, non-cystic (Table 7). Chromophob adenoma was the most common (56.3%) followed by acidophilic adenomas (41.8%). Histologically (90.9%) of pituitary adenomas were benign, while aggressive (invasive) pituitary adenoma was seen in (9.1%) (Table 8).

Table 7: Texture and consistency of the adenoma

Texture and consistency	No.	Percent
Cystic	8	14.5
Non cystic (solid)	47	85.4
Soft	49	89
Firm	6	10.9

Table 8: Histopathological results of pituitary adenomas

Histopathology	No.	Percent
Acidophilic	23	41.8
Chromophob	31	56.3
Basophilic	1	1.8
Aggressive	5	9

Five patients had aggressive adenomas; all were acidophilic adenomas, firm, and highly vascular. All had suprasellar and lateral extension (Table 9).

Table 9: Staining, vascularity, texture and extension of aggressive pituitary adenomas

Histopathology	Vascularity	Texture	Extension
Acidophilic	High	firm, non-cystic	superior & lateral
Acidophilic	High	firm, cystic	superior & lateral
Acidophilic	High	firm cystic	superior & lateral
Acidophilic	High	firm, non-cystic	sup., ant., & lateral
Acidophilic	High	firm, non-cystic	superior & lateral

Dramatic improvement of the visual fields and acuity was documented in 25 of 30 patients (83.3%). Improvement in the cranial nerve deficit with diplopia was seen in (50%). Patients with sever visual impairment, and advanced optic atrophy did not show similar improvement, but no one got worse (Table 10).

Table 10: Post-operative visual improvement

Improving sings and symptoms	No.	Percent
Visual field and acuity	25/30	83.3
Diplopia and squint	2/4	50
Ptosis	1/1	100

Right sub frontal craniotomy was the approach used in 46 patients (83.6%) and trans-sphenoidal approach was performed in 9 patients (16.4%). Gross total resection of the tumor (capsular) was achieved in 29.1% (Figure 4) and subtotal resection (intracapsular) in 70.9%. Benign chromophobe adenoma was the commonest pathological finding, which accounted for 56.3%of cases, followed by acidophilic adenoma in 41.8%. While all aggressive pituitary adenomas were acidophilic and account about 9% (5 patients).

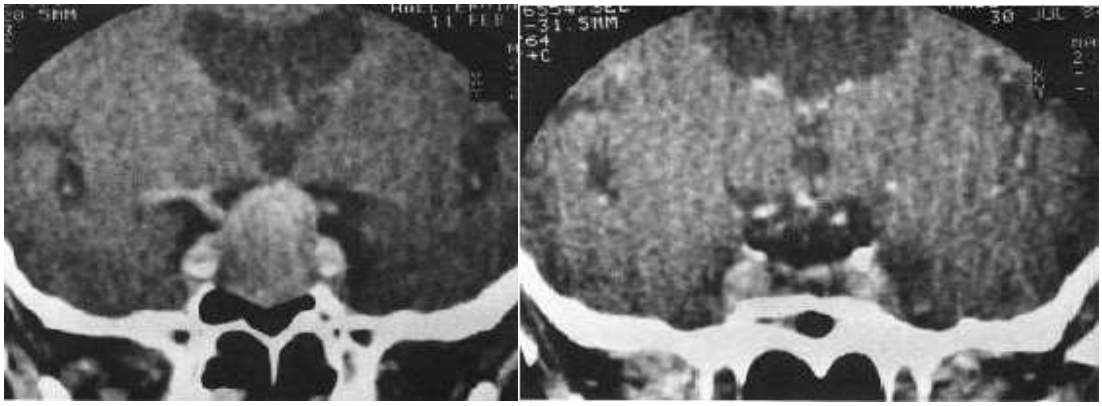

Figure 4: Brain CT scan (coronal sections) of pituitary adenoma showing suprasellar extension (Pre- operative Lt. and post operative Rt.)

All aggressive adenomas had postoperative radiotherapy (all of them did not complete their course) however three of them had recurrences after one year, there was no relation between recurrence and the type of adenoma or the extent of surgical resection. Early postoperative complications (Table 11) included diabetes insipid (DI) in 6 patients, 2 of them following trans-sphenoidal approach, and fortunately only one patient had permanent DI who need permanent antidiuretic hormone (DDAVP) treatment.

Table 11: Post-operative complications

Complication	Approach	No.	Percentage	Percentage from total
CS leak + meningitis	Transcranial	1/46	2.1	1.8
Infected wound	Transcranial	1/46	2.1	1.8
Diabetes Iinsipidus	Transcranial	4/46	8.6	10.9
	Trans sphenoidal	2/9	22.2	
Hypothyroidism	Transcranial	4/46	8.6	7.2
Unilateral anosmia	Transcranial	46/46	100	83.6
Hematoma	Transcranial	1/46	2.1	1.8
Recurrence	Transcranial	3/46	6.5	5.4
Post radiotherapy glioma	Transcranial	2/46	4.3	3.6
	(Previous op.)			
Death	Transcranial	3/46	6.5	5.4

Recurrent CSF leak and meningitis was detected in one patient who transcranial surgery for aggressive pituitary adenoma. Wound infection was recorded in one patient. Hypothyroidism, proved by hormonal assay was recorded in 4 patients (7.2%). Intracerebral hematoma detected in one patient who died in the third postoperative day. Two other patients died one of them developed pulmonary embolism and the other had hypothalamic ischemia. Post radiotherapy glioma proved by histopathology was recorded in 2 patients from a total of thirty-seven who had radiotherapy (5.4%).

Discussion

In Large series of intracranial neoplasm (Burrow et al., 1981; Kovacs et al., 1986)[8,9], pituitary adenomas comprise about 10-15 percent of brain tumors. The true incidence in Iraq is unknown.

Regarding the sex distribution, pituitary adenomas are equally distributed between the sexes. From series (Minderman et al., 1994)[10] one notes a slight female predominates in prolactin hormone (PRL), thyroid stimulating hormone (TSH), and adrenocorticotropic hormone secreting adenomas, whereas male dominance was recorded in growth hormone (GH) secreting adenomas, and non-functioning pituitary adenomas. Equal sex distribution is found in older patients. In our study, slight male preponderance (56.3%) was recorded.

Pituitary adenomas are more apt to be found in specific age groups. They are tumors of the middle decades of life, although isolated examples have been reported in children with pituitary adenomas. One also notices that the average age in lower in acidophil adenomas than chromophobe adenomas[11-13]**.** The results in this study are very similar to the published figures.

Symptoms and Signs

The signs and symptoms of pituitary adenomas are produced by the local mass effect of the adenoma and by the systemic manifestations, which are related to the hormonal disturbances.

In this study non-functioning pituitary adenomas comprise about (54.5%), whereas functional pituitary adenomas were found in (45.5%). Sassolas et al., (1993), and Nedvidkova et al., (2000)[14,15] found non-functioning adenomas in only 40% of cases. This may be due new and more thorough hormonal analysis.

The signs and symptoms produced by the space occupying effect are due to the direct pressure or invasion of the adjacent parasellar structures and the optic nerves and chiasm.

We found the most common symptom was headache (90.9%), the cause of the headache is stretching of the diaphragma sellae, However many of the cases with headache, especially females with hormonal disturbances have psychological cause for their headache. Generally the reported incidence of headache is about 40%[15-17]. The headache is often non-specific, found primarily in the vertex as a dull ache, and does not change with position. In pituitary apoplexy however headache is sudden, severe and is accompanied by neck stiffness.

Visual deterioration was found in 78% of cases, in which decreased visual acuity was detected in all of them, while visual field defect (uni or bitemporal hemianopia) was found in (62.3%)of cases. Comparing the results with other series of Sassolas et al., (1993); Fajardo (1982), and Burrow et al., 1990[14.17,18], visual defect was reported in about 50-70% of patients, at the time of diagnosis. The higher incidence of visual deterioration probably indicates late presentation.

Primary optic atrophy was found in 29% of cases, whereas papilledema was detected in (12.7%) of patients, which is high compared with the reported incidence of 6% by Chang et al., (2000)[19]. However the

typical visual field defects seen in some of these patients with reported papilledema suggest that the impression made by junior residents was false.

The reported incidence of cranial nerve palsies other than the optic nerve is 5-17%. Usually the 3rd, 4th 6th and less commonly the 5th nerves are involved[11-13]. Generally cranial nerve palsies suggest lateral extension into the cavernous sinus, and is mostly associated with aggressive adenomas. The 4 patients who had cranial nerve palsies (7.2%) all had lateral extension and all were aggressive tumors.

Regarding epilepsy, seizures were reported in 1-10% of patients with pituitary adenoma. Most series[11,12,20] in this study it was noticed in one patient (1.8%), We could find no reason or association between epilepsy and the pathology or extension of the tumor.

Hypopituitarism, according to many series, was seen in a good proportion of patients. One important feature for example is Insufficient gonadotropic hormone secretion, which was found in 50-90% of patients (Bakay, 1950 and Arafah et al., 1986)[11,21] In this study only one patient was diagnosed to have hypogonadism due to deficient gonadotropic hormone (GnH) secretion, confirmed by hormonal assessment (1.8%). This lowly incidence of hypogonadism in males, is probably only apparent, due to denial of patient for social reasons, and failure on the part of physicians to asses this important clinical feature of pituitary adenomas.

Regarding functional pituitary adenoma, we found that hyperprolactinemia comprises 72% (32% from total number), by comparing our results with those of other studies (Visot et al., 2001, Davis et al., 1985 and Kleinberg, 1983)[22-24]. We found prolactin secreting adenomas comprising 25%. From this we expect that the higher percentage was not due to pure PRL producing adenoma rather than secondary hyperprolactinoma due to local mass effects causing amenorrhea - galactorrhea Syndrome primarily in females and loss of libido with impotence in males.

Growth hormone (GH) secreting adenoma detected in 64% of patients with functioning pituitary adenomas (29% from total) in which acromegalic features detected in all of them , whereas gigantism detected in only one patient (4%), which is exactly the same percentage found in other series. Insulin dependent diabetes mellitus (IDDM) detected in 62% of patients with Acromegaly, Compared with about 50% reported in literatures. Hypertension detected (37.5%) similar with other studies 36% (Jackson et al., 1999)[25].

Cushing's disease was found in 4% of functioning pituitary adenomas (1.8% from total), which is almost the same of other series (Tindall et al., 1985 and Sheithauer et al., 1986)[2,26]. This disease is rare, and because most of them are due to a microadenoma (80%) it rarely gives rise to other hormonal or compression symptoms.

In our study, no patient was found to have hyperthyroidism or excessive secretion of GnH, which indicate their rarity as seen in other series, TSH producing adenoma comprising about 1% (Martin et al., 1977, Black et al., 1984, Linfoot et al., 1979, and Post et al. 1980)[13,27-29].

Radiological investigations

The radiology of the sella tursica is an interesting subject when considering pituitary adenomas, in plane x-ray, non-functional pituitary adenoma enlarge the sella almost without exception. We had three patients in our study that had normal sized sella tursica (5.5%).With high resolution Brain CT scan, microadenomas can be correctly identified in 70% of cases, and the CT scanner was accurate in the detection of macroadenomas in 95% of cases. (Chang et al., 2000)[19], most of which highly enhances with contrast study.

In this study we found most of pituitary macroadenomas were isodense (76%), while they were hyperdense in 17.3% of patients. Good enhancement with contrast study was seen in 85.7% and by comparing these results with those of other studies we found it similar (Chakeres et al., 1990 and Leeds et al. 1977)[30,31].

Histopathology

On the basis of staining properties of the cell cytoplasm, pituitary adenomas were previously defined as one of three morphological entities, chromophobic, acidophilic and basophilic adenomas. Since the tincturial characteristics of the adenoma cells cannot be correlated reliably with the cell type, secretary activity or cytogenesis, this basis for classification is no longer considered useful (Kamal et al., 1995)[1].

In spite of what is said above, above, our histopathological labs continue to use the same type of morphological classification according to the staining property with hematoxylin and eosin, which revealed that chromophobe adenoma comprise about 56.3%, whereas acidophilic adenomas account for 41.8% and basophilic adenomas 1.3%. By comparing with other series (Wilson et al., 1978 and Tindall et al., 1995, found that chromophobe adenomas account for 75%, whereas acidophilic adenomas about 17%[32,33], this indicate that in our study chromophobe adenoma is much less, this could be due to the poor preparation of the histopathological section. Regarding basophilic adenomas, the result coincides with those of other series of 1-2%.

Macroscopically the consistency of pituitary adenomas is classified into either cystic (partial or complete) and solid. In this study, pituitary adenomas were cystic in 14.5% which is somewhat similar to those of other studies (18-20% by Asa et al, 1993)[34].

Regarding the texture, soft suckable pituitary adenoma was detected in 89%, which is almost the same compared with other series, (92% by Kamal et al., 1995)[1].

Aggressive invasive pituitary adenoma was detected in 9.1% of all types of pituitary adenomas, 50% of them were acidophilic.

Operative findings and surgical management

Regarding the optic chiasm, normal position of the chiasm was found in 89.1%, prefixed chiasm in 2.1% and postfixed chiasm in 8.6% of cases. By comparing with other studies, the percentage were 80%, 9% and 11% respectively (Tindall, 1995)[33], and 70%, 15% and 15% respectively (Albert et al., 1995)[35] which indicate approximately similar results. Regarding extension of the pituitary adenomas we detected that during operation the incidence of tumor extension was 86.9%. Whereas preoperative C.T scan reported 82.6% tumor extension. This indicates that C.T scan is not 100% accurate in the diagnosis of extension.

In the series of Wilson & Demsey (1978)[32], 48.4% pituitary adenomas were confined to the sella tursica, significant suprasellar extension was observed in 34.8%, infrasellar extension in 17.6% and both in 6.8% of cases. In this study, suprasellar extension was seen in 86.6%, whereas infrasellar extension in 22.2% of cases. The increase in the incidence of suprasellar extension may reflect a delay in the diagnosis, and the higher number of non-functioning pituitary adenomas.

As regard to the surgical outcome in both approaches, many series were reviewed regarding the mortality rate and these were ranging from 1.4 - 35% in transcranial subfrontal approach, and from zero to 1.5% following trans-sphenoidal approach (Tindall et al., 1986)[2]. In our study, 3 patients died (5.4%) all of them following transcranial approach, while there was no mortality following trans-sphenoidal approach.

Regarding patient's condition following the operation we found that 83.3%

of patients have improved vision, which is a good result compared with the reported improvement rate of 41-90%[11,19,36].

Tumor recurrence was recorded in 3 patients (6.5%) following transcranial approach, with no recurrence following trans-sphenoidal approach. The previous histopathological results of those with recurrent adenoma were of invasive character, and all had radiotherapy. The result is quite good compared with those registered from other series, which ranged between 6 and 11%, usually following transcranial approach of highly invasive adenoma (Linfoot, 1979; Ciric, et al, 1983; Domingue, et al., 1980; Faria, et al., 1982)[28,36-38]. Invasiveness was the only factor that was associated with recurrence, which raises question regarding the necessity and effectiveness of conventional radiotherapy. Postradiotherapy (glioma) was detected in 2 patients(3.6%), which is similar to other series (George, et al., 1995 and Fajardo, et al., 1982)[33,39].

Conclusions

1. Pituitary adenoma is usually benign relatively avascular soft in consistency with characteristic clinical and radiological features, commonly present in 4th decade.
2. Hyperprolactinenia was the most common hormonal disturbance, and visual deterioration was the most common presenting symptom.
3. Regarding the postoperative prognosis, unless associated advanced primary optic atrophy, there was dramatic improvement in the optic nerve function (83.3%), and other cranial nerves function (50%), which indicate that the primary lesion is due to the pressure effect rather than invasion.
4. Diabetes insipidus is the commonest postoperative complication especially following trans-sphenoidal approach (10.9%) and it is transient in most cases.
5. Tumor invasiveness was the only factor that was found to be associated with recurrence of pituitary adenoma.
6. Postoperative radiotherapy should be considered for invasive adenomas; however the risk of tumor genesis makes one think of an alternative treatment such as Gamma knife surgery.

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