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Original Article

Etiology, functional status and short term outcome of patients with Pituitary lesions. An experience from a developing country

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Abstract

Objective: To describe the etiology, functional status and short term outcome of patients with pituitary lesions (PL).

Methods: Brain or pituitary MRI reports of 3,753 patients were analyzed for PL over the period of 2000 to 2007, done at the Aga Khan University Hospital (AKUH), Karachi, Pakistan. MRIs with reported PL and all those ordered by Endocrinologists with or without pituitary abnormalities, were included in the analysis. This made a total of 338 (9%) MRI reports. PL were defined as pituitary tumors, cysts, haemorrhage, hypoplasia; and empty sella. Patients with these PL, were analyzed for symptoms, hormonal profile and short term outcome in the hospital retrospectively.

Results: In the analysis of 338 MRI reports, 23% had normal pituitary gland on MRI examination. Hypogonadotrophic hypogonadism was the commonest (38.5%) endocrine abnormality seen with normal pituitary MRI, followed by hypopituitarism (5.1%). Most common PL identified were macroadenoma (38.7%), empty sella (16.5%) and microadenoma (12.7%). Patients with macroadenoma had 58% of non-functional tumours while 19.1% had hypopituitrism, 17.6% had acromegaly and 17.5% had prolactinoma. Majority of these lesions were causing headache and visual symptoms (42.7%) and were treated with surgery (75.5%). Patients with microadenoma included 39.5% prolactinomas, 18.6% cushing disease, 14% acromegaly, 4.7% hypogonadotrophic hypogonadism and 2.3% hypopituitrism. Majority of these lesions were treated with drugs and 37.3% were treated with surgery. In empty sella patients, 32% patients had endocrine abnormalities among which 21.4% had hypopituitrism, 2% had hypogonadotrophic hypogonadism, and only 6% patients had normal endocrine workup. A significant number of patients (62.5%) never had endocrine hormonal checkup.

Conclusion: Although PL are less common entities (9% in 3,753 reports) but they are associated with significant endocrinal abnormalities and need prompt treatment. Empty sella, which is not considered as a distinct abnormality, is also associated with significant endocrine deficiencies (JPMA 59:839; 2009).

Introduction

Hypothalamic-pituitary lesions present with a variety of manifestations, including pituitary hormone hypersecretion or hypo-secretion, sellar enlargement and visual loss. Among them, pituitary tumours are the most common intracranial neoplasm accounting for 10.7% of primary central nervous system tumours. They are classified by size (microadenomas < 10 mm and macroadenomas > 10 mm) and according to their ability to produce hormones (functioning or nonfunctioning adenomas). Prevalence studies suggest pituitary adenomas are common in the normal population and were present in between 1% and 35% of pituitaries studied at autopsy and in 1% to 40% of patients undergoing an MRI scan for reasons other than to assess the hypothalamic-pituitary axis. The prevalence of macroadenomas was estimated to be 0.16% to 0.20%.[1]

Empty sella, which is also considered a distinct lesion of pituitary gland, occurs when the subarachnoid space extends into the sella turcica, partially filling it with cerebrospinal fluid. This process causes remodeling and enlargement of the sella turcica and flattening of the pituitary gland. The presence of an empty sella does not exclude the possibility of a coexisting pituitary tumours.[2]

Existing epidemiological data suggest that the incidence of pituitary adenomas is rising, although it is difficult to determine whether this is due to widespread access to magnetic resonance imaging (MRI) and accurate biochemical testing, leading to improved recognition of clinically relevant pituitary tumours.[3]

The true prevalence of pituitary lesions in our region is conflicting and discordant. To date, there is no local experience of etiology and endocrinal status of patients with pituitary lesions therefore, current study is designed with the aim to describe the etiology, functional status and short term outcome of patients with pituitary lesions, presented to a single tertiary care center in Pakistan.

Materials and Methods

This study was done in the Aga Khan University Hospital (AKUH), Karachi Pakistan, over the period of 2000 to 2007. During this time period, 9000 gadolinum enhanced MRIs

of brain including pituitary were performed in the Radiology department of the AKUH. Each MRI was read by an experienced consultant Radiologist and report was saved in hospital computer database. We obtained the list of these MRI reports and analyzed 3,753 MRIs ordered by Endocrinologists (367), Neurologists (2379), Neurosurgeons (910) and Ophthalmologists (95).

MRIs with reported pituitary lesions and all those ordered by Endocrinologists with or without pituitary abnormalities, were included in the analysis. This made a total of 338 (9%) MRI reports available for review.

Pituitary Lesions reported on brain or pituitary MRIs, were defined as pituitary tumours (pituitary microadenoma when size ≤ 1 cm; pituitary macroadenoma when size ≥ 1 cm), cysts, haemorrhage, hypoplasia; and empty sella. Empty sella was diagnosed when there was absence of pituitary gland on the radiographic image (MRI). Patient charts were reviewed and necessary information regarding demographics, hormonal profile and outcome was collected. Short term outcome was taken as initial treatment patient was given in the hospital before discharge.

Functioning pituitary tumours represented tumours which secrete one or more hormones from the pituitary gland resulting in the symptoms and signs of the hormone excess. Non-functioning pituitary lesions represented tumours which do not secrete any hormone and sometimes can cause inhibition of the hormones secreted by the pituitary gland, due to the mass effect.

All laboratory values were interpreted based on the reporting laboratory's normal range, unless stated otherwise. Hormonal assays were done using standard radio-immunoassay methods. Acromegaly was diagnosed on the basis of clinical features and high IGF-1 and positive Oral glucose tolerance test with growth hormone. Cushing's disease was diagnosed when there was high ACTH and inappropriate suppression of cortisol (> 50%) on high dose dexamethasone suppression tests. Hyperprolactinaemia was defined as prolactin (PRL) elevation (upper limits of normal ranged from 22 µg/L depending on laboratory). Hypogonadotropic hypogonadism was diagnosed when estradiol or testosterone levels were low in the presence of inappropriately normal or low FSH and/or LH levels. Hypopituitarism included deficiency of the GH (evoked GH <3 ng/mL), gonadal (FSH/LH), thyroid (abnormal thyroid hormone levels with inappropriate TSH levels), adrenal (blunted cortrosyn responses) axes, and/or panhypopituitarism. Thyrotropinoma (secondary hyperthyroidism) was diagnosed when there was thyrotoxicosis with inappropriately normal TSH. Diabetes insipidus was diagnosed on the basis of clinical features with high serum osmolality and low urine osmolality and response to desmopressin. Isolated Growth hormone deficiency was diagnosed using measurement of low IGF-1 (with respect to age and gender) and Insulin tolerance test with growth hormone (with peak response of growth hormone less than 10 ng/dl in hypoglycaemia), in the presence of normal hormonal profile.

Results

In the analysis of 338 MRI reports, Figure shows the MRI details of different pituitary lesions found. There were 23% reports who had normal pituitary, and endocrinal

Table-1: Characteristics of patients with normal and 3 common pituitary lesions.

Normal Pituitary (n = 78, 23%)	
Age (mean, years) : Range in years	31.1±14.1 : (12 – 74)
Males / Females	35 (45%) / 43 (55%)
Endocrinal abnormalities	
None *	9 (11.5%)
Hypogonadotrophic Hypogonadism	30 (38.5%)
Hypopituitarism	4 (5.1%)
Hyper-prolactinemia	17 (21.8%)
Cushing's Syndrome	2 (2.6%)
Secondary Hypothyroidism	2 (2.6%)
Isolated Growth hormone deficiency	2 (2.6%)
Not Known	9 (11.5%)
Pituitary Macroadenoma (n = 131, 38.7%)	
Age (mean, years) : Range in years	44.36±16.54 : (12 – 84)
Males / Females	64.9% / 35.1%
Non Functional Tumours	77 (58%)
Endocrinal abnormalities	
None	28 (21.4%)
Hypopituitarism	25 (19.1%)
Not known	14 (10.7%)
Prolactinoma	25 (19.1%)
Acromegaly	23 (17.6%)
Cushing's Disease	1 (0.8%)
Thyrotropinoma	2 (1.5%)
Hypogonadotrophic Hypogonadism	2 (1.5%)
Diabetes Insipidus (post-operative)	5 (3.8%)
Pituitary Microadenoma (n = 43, 12.7%)	
Age (mean, years) : Range in years	34.12±13.5 : (14 – 66)
Males / Females	32.6% / 67.4%
Non Functional Tumours	6 (13%)
Endocrinal abnormalities	
None	3 (7%)
Prolactinoma	17 (39.5%)
Acromegaly	6 (14%)
Cushing's Disease	8 (18.6%)
Pan-hypopituitarism	1 (2.3%)
Unknown	6 (14%)
Hypogonadotrophic Hypogonadism	2 (4.7%)
Empty Sella (n = 56, 16.5%)	
Age (mean, years) : Range in years	55.63±14.82 : (12 – 78)
Males / Females	28.6% / 71.4%
Endocrinal abnormalities	
Not investigated	35 (62.5%)
Hypopituitarism	12 (21.4%)
None	3 (5.4%)
Hypogonadotrophic Hypogonadism	2 (3.6%)
Growth Hormone deficiency	1 (1.8%)
Other Endocrinal Abnormalities	3 (5.4%)

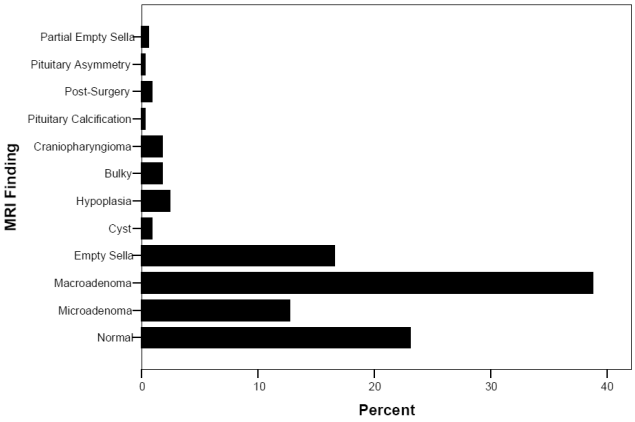

Figure: Graph showing frequencies of various pituitary lesions.

evaluation of these patients revealed 38.5% had hypogonadotrophic hypogonadism, 5.1% had hypopituitrism and 2.6% had isolated growth hormone deficiency. The major pituitary lesion found was Pituitary Macroadenoma (38.7%). We divided the patients with pituitary lesions into a) Pituitary Macroadenoma, b) Pituitary Microadenoma and c) Empty Sella. Details of these lesions are given in Table-1. Table-2 shows various hormonal abnormalities associated with common pituitary lesions of our study.

Pituitary Macroadenoma (n = 131):

In the patients with these lesions, males predominate, with a male to female ratio of ratio of 1.8:1. Etiology of these lesions is given in Table-1 and 2.

Majority of the patients had non-functional pituitary tumours (NFPT) (65%, n=86) resulted in endocrinal disturbances in 48% (n=42) of cases. Table-3 shows different characterisitics of non-functioning tumours. Visual symptoms along with headache (42.7%) were the predominant presenting symptoms of these patients other than symptoms related to hormonal hyposecretion. Regarding treatment, trans-sphenoidal pituitary surgery was done in 99 (75.5%) patients, 10 (7%) patients were referred for radiotherapy after surgery, 5 (3%) patients were put on hormone replacement therapy and patients with Prolactinoma were treated with dopamine agonists (14.3%).

Patients with NFPT (n=86) had a mean age of 46±15.2 years with male predominance (63% males, 37% females). Their main presenting symptoms were visual deterioration (24.4%) and headache (10.5%). Nearly 37.2% had no hormonal abnormality while 30.2% had hypopituitarism, 2.3% had hyperprolactinoma and secondary hypothyroidism.

Pituitary Microadenoma (n = 43):

The mean age of these patients was 34.12±13.5 years (Range: 14 - 66) years with male to female ratio of 1:2. Etiology is given in Table-1 and 2. Symptoms of these patients related to the type of endocrinal hyper or hyposecretion. None of the patient had visual symptoms, however headache is present in 7 (16%) cases. Regarding treatment, trans-sphenoidal pituitary surgery was done in 37.3% of patients, in which 14.2% had acromegaly and 20% had cushing's disease. Rest of the patients, of whom majority had prolactinoma, were treated with dopamine agonists.

Table-2: Endocrinopathies and associated pituitary lesions.

Endocrinal Abnormality* (n)	Normal MRI (%)	Macro-adenoma (%)	Micro-adenoma (%)	Empty Sella (%)	Cranio-pharyngioma (%)	Others (%)
None (53)	9 (17)	28 (52.8)	3 (5.7)	3 (5.7)	-	10 (18)
Acromegaly (30)	-	23 (76.7)	6 (20)	-	-	1 (3.3)
Cushing's disease (11)	2 (18/2)	1 (9.1)	8 (72.7)	-	-	-
Hyper-prolactinemia (59)	17 (28.8)	25 (42.4)	17 (28.8)	-	-	-
Thyrotropinoma (2)	-	2 (100)	-	-	-	-
Hypopituitrism (51)	4 (7.8)	25 (49)	1 (2)	12 (23.5)	5 (9.8)	4 (7.9)
Hypogonadotrophic hypogonadism (40)	30 (75)	2 (5)	2 (5)	2 (5)	-	4 (10)
Secondary Hypothyroidism (5)	2 (40)	1 (20)	-	-	-	2 (40)
Isolated Growth Hormone deficiency (3)	2 (66.7%)	-	-	1 (33.3)	-	-
Secondary Adrenal Insufficiency	1 (20)	2 (40)	-	1 (20)	1 (20)	-
Not Known (65)	9 (13.8)	14 (21.5)	6 (9.2)	35 (53.8)	-	-

*Rest of the Endocrinal abnormalities not shown.

Patients with Empty Sella (n=56):

The mean age of patients was 55.63±14.82 (Range: 12-78) years with male to female ratio of 1:2.5. Etiology is given in Table 1 and 2. Majority of these patients had brain MRI done due to other reasons and found to have empty sella. Among these patients, 37.5% (n=21) had unconsciousness with low blood pressure, 19.6% (n=11) had headache, 10.7% had menstrual disorders, weight loss and 7.1% (n=4) had hyponatraemia. Hormonal abnormalities were found in 32% patients, while 62.5% patients were not evaluated for hormonal abnormality. Only 43% patients had consultation from Endocrinology Department. Patients having hormonal abnormalities were treated with hormone replacement therapy.

Discussion

The present study revealed that 1) Pituitary macroadenoma were the most common pituitary lesions, 2) Majority of the macroadenomas were non-functional tumours (NFPT), 3) In pituitary microadenoma, prolactinoma were the most common endocrinal abnormality, 4) Patients with Empty sella syndrome had a significant number of endocrinal abnormalities, and majority of them were never investigated, 5) Craniopharyngioma were uncommon tumours in adults, 6) Visual symptoms were common in patients with macroadenomas, and 7) Surgery was the common treatment modality in pituitary macroadenoma.

Since all MRIs ordered by Endocrinologists were included in the study, we saw a reasonable number of patients with normal pituitary MRI report. Most of these patients (75%) had hypogonadotrophic hypogonadism without any other hormonal abnormalities. These patients were labeled as having isolated idiopathic hypogonadotrophic hypogonadism. Our findings are similar with the previous studies showing that majority of these patients had normal MRI.[4] MRI of the brain is necessary to exclude a pituitary tumours, a prolactinoma or craniopharyngioma.[5] In the absence of a tumours, the cause is generally thought to be hypothalamic or idiopathic by exclusion.

Prolactinoma's and non functional pituitary tumours were the highest pituitary lesions found in our study which is in-concordance with the previous studies.[1,3] In our series, prolactinoma's in general, were seen more in male patients with pituitary macroadenomas, while in females, they were more in microadenomas. This is probably due to the fact that females present early due to their symptoms of menstrual disorders and glactorrhea. This finding is also similar to the previous studies on prolactinomas.[6]

There are reasonable number of patients with hypopituitarism (n=51), commonly associated with macroadenoma (49%), followed by empty sella syndrome (23.5%) and craniopharyngioma (9.8%). Tomlinson JW et al,[7] in their study, showed that non-functinong pituitary tumours (57%) and craniopharyngioma (12%) were the major causes of hypopituitarism, while empty sella syndrome contributed 2%. His findings are somewhat similar to our findings except empty sella syndrome which contributed significantly in our study.

Acromegaly is another common functional pituitary disease seen in our series as well. Majority of these patients had pituitary macroadenoma. A regional study from an endocrine referral center, in Srinagar, Kashmir,[8] reported highest frequency of acromegaly in their series, which also reported more patients with macroadenomas. We also had two cases of thyrotrophinomas, both had macroadenoma and were treated with trans-sphenoidal surgery.

Clinically NFPT are the major group in the patients with macroadenoma (65%) and mostly associated with visual symptoms, headache and endocrinal dysfunction associated (48%) with the compression effects on the normal pituitary gland. This finding is comparable with other studies.[9,10] The endocrinal evaluation given in Table-3, does not show the associated growth hormone deficiency, because it was not checked in any case in our series. The multitude of studies performed on such patients, in recent years shows the potential benefit of GH therapy in GH-deficient adults suggest that GH testing should be done in all such patients.[11]

We saw a significant number of cases (16.5%) who had empty sella syndrome, found mostly on brain MRIs done for other reasons. Only one case had secondary empty sella after surgery, while rest of them had primary empty sella. Primary empty sella syndrome which results from congenital incompetence of the diaphragma sellae is common, with an incidence in autopsy series ranging from 5 to 23%,[12] which is similar to our series as well. Although, endocrine abnormalities are not a common occurrence in these cases, 32% of our cases had endocrinal abnormalities. There are several papers and case reports which showed hormonal abnormalities associated with empty sella and termed as "empty sella syndrome."[12-15] One large published series of 213 patients of empty sella syndrome reported prevalence of endocrine dysfunction as 19%.[16] Another finding which was related to our series was predominance of females in such cases.[13] Rarely, empty sella syndrome is also associated with hormone excess possibly due to coexisting micro-adenoma within the compressed gland,[17] although we did not come across such a case in our series.

Another noteworthy finding in our series is that 62.5% of patients of empty sella syndrome were not investigated for any endocrinal abnormality and 43% were sent for endocrinologist consultation only. The reason could be lack of unawareness and knowledge regarding the empty sella syndrome by most of the physicians and surgeons treating such patients.

Craniopharyngiomas which are considered a common sellar tumours in the literature[18] especially in childhood populations and half of the total cases in adults, were not commonly seen in our study. One of the reason behind is that we did not include paediatric population in our study, secondly, we do not have any epidemiological data which supports that craniopharyngiomas are common sellar tumours in our region as they are in the western countries. Our later assumption is also somewhat supported by a regional study reported from Kashmir, which showed no cases of craniopharyngioma in their study.[8]

There are several limitations of our study. First of all it is a retrospective data taken from the patient charts. Secondly, some of the patients are not evaluated for any endocrine dysfunction (especially in empty sella cases) at all. Thirdly, follow-up of the patients was limited.

Conclusion

To conclude, PL are less common entities in the present study but they are associated with significant endocrinal abnormalities and need prompt treatment. Non functional pituitary macroadenomas causing visual impairement needed prompt surgery (except prolactinomas in some cases). Functional pituitary microadenomas also needed surgical treatment except prolacinomas. Majority of the patients with hypogonadotrophic hypogonadism have normal pituitary glands. Empty sella, which is not considered as a distinct abnormality, is also associated with significant endocrine deficiencies and it is recommended that all patients with empty sella should be referred to endocrinologists for assessment.

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