Clinical and endocrine aspects of pituitary tumors

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ABSTRACT

Objective: To study the clinical spectrum and endocrine profile of pituitary tumors presenting to a tertiary care endocrine center.

Methods: Retrospective analysis of clinical and hormonal data of patients with pituitary tumors admitted in the Endocrinology Department of Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Kashmir India between January 1989 and December 1998.

Results: Over a period of one decade, 75 subjects were diagnosed to have pituitary tumors. Somatotroph adenoma was the most common pituitary mass lesion seen (44/75) and followed in the decreasing order of frequency, by non-functioning pituitary tumor (12/75), prolactinoma (11/75) and corticotroph adenoma (8/75). Overall there was a male preponderance (male to female ratio was 41:34). Subjects with somatotroph adenoma presented with classical features of acromegaly: mean fasting and post glucose suppression growth hormone levels were 34.04±11.67 and 36.47±6.64 ng/ml. Eleven subjects (9 females and 2 males) had prolactinoma; females presented with the classical symptom complex of amenorrhea-galactorrhea while males presented with headache, visual disturbances and impotence. The 12 subjects with nonfunctioning pituitary tumors presented with features of mass lesion. Of the 8 subjects (6 females and 2 males) with corticotroph adenomas, 2 were confirmed to have periodic hormonogenesis.

Conclusion: In an endocrine center, functioning pituitary tumors are more often seen than non-functioning tumors.

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Pituitary tumors constitute 10-15% of intracranial tumors in surgical specimen.[1] Patients with pituitary tumors present with symptoms of a mass lesion, endocrine dysfunction or both. Endocrine dysfunction may be hyperfunction, hypofunction or both. Patients usually are referred to an endocrine service with a symptom complex resulting from hormone deficiencies or excess. With the proliferation of newer imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI), clinicians increasingly encounter incidental findings consistent with the diagnosis of a pituitary microadenoma. We retrospectively analyzed the data of subjects diagnosed to have pituitary tumors. In this study we describe the clinical and endocrine aspects of these patients.

Methods. Records of patients admitted with pituitary tumors in the Endocrinology Department of Sher-i-Kashmir Institute of Medical Sciences Srinagar Kashmir, India from January 1989 to December 1998 were thoroughly analyzed. Out of the initial screening of 87 subjects, records of 12 subjects were incomplete and were excluded from the study. The remaining 75 subjects constitute the

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subject material for the study. Information was mainly collected from 2 sources such as case records of subjects of pituitary tumors admitted under the endocrine services and computerized data of hormonal analysis of the above subjects. Records were thoroughly reviewed for clinical data and hormonal assays. Basal investigations including complete blood count, urine examination, biochemical tests including blood urea nitrogen, serum creatinine, venous plasma glucose, serum calcium, phosphorus, alkaline phosphatase, total protein, albumin and liver enzymes were performed in every patient. An electrocardiogram, x-ray chest and x-ray skull and CT scan of pituitary was also performed in every subject. Magnetic resonance imaging was carried out in those subjects suspected to have a pituitary tumor with a normal or inconclusive CT scan of pituitary. On plain x-ray, skull pituitary fossa was considered enlarged if lateral sellar volume (anteroposterior length multiplied by depth of pituitary fossa was >130 sq mm).[2] Basal hormones including triiodothyronine, tetra-iodothyronine, thyroid stimulating hormone (TSH), growth hormone (GH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL) and cortisol were estimated in every subject. Growth hormone excess was diagnosed if the serum GH was >2 ng/ml, 60 minutes after oral administration of 100 gm of glucose.[3] Cushing's disease was diagnosed by dexamethasone suppression tests.[4] Prolactinoma was diagnosed if fasting serum prolactin was >200 ng/ml.[3] Subjects without clinical or biochemical evidence of hormone excess with radiological evidence of a pituitary mass were diagnosed as having non-functioning pituitary tumors (NFPT). An ophthalmological evaluation was carried out in every subject including testing for visual acuity, fundus examination and perimetry. All hormone estimations were performed with specific radio-immunoassay. Serum concentrations of TSH and LH were estimated using the commercially available kits (Bharat Radiation and Isotope Technology, Mumbai, India). The rest of the hormones were estimated using radioimmunoassay kits obtained from Diagnostic Products Corporation (Los Angeles, CA, USA). Subjects with evidence of polyuria were subjected to dehydration test.

Results. Over the 10-year period, 75 subjects (41 males and 34 females) were diagnosed to have pituitary tumors. The age at presentation ranged between 17 and 70 years. Most of the subjects (39/75, 52%) presented in third and fourth decades of life. Four types of pituitary tumors were seen such as somatotroph adenoma, prolactinoma, and non-functioning pituitary corticotroph adenoma. Forty-four subjects (56.6%) were diagnosed to have somatotroph adenoma. **Table 1** summarizes the presenting features and hormonal data in subjects with somatotroph adenoma. All subjects had somatic features of acromegaly including enlargement of hands and feet, soft tissue swelling and prognathism; 31.8% of patients had headache. Other symptoms or signs were encountered less frequently. Two subjects were prepubertal and presented with tall stature and features of hypogonadism. Overall mean age at presentation was 41.23±11.78 years. Males presented slightly earlier at the mean age of 39.57±10.73 years as compared to females (44.13±13.30 years). Thirty-one subjects were detected to have hypertension. Mean systolic blood pressure was 146.92±16.01 mm Hg in males and 130±18.71 mm Hg in females. Diastolic blood pressure was 95.45±6.88 mm Hg in males and 84.11±11.40 mm Hg in females. Four subjects had diabetes mellitus (DM) and 3 had impaired glucose tolerance. Overall mean fasting blood glucose was 85.58±11.48mg/dl and 2 hours postprandial was 156.90±41.19 mg/dl in those subjects who were not known diabetics. None of the subjects had hypercalcemia. On plain x-ray skull, mean lateral sellar volume was 183.9±53, 18 sq.mm. Contrast enhanced CT revealed pituitary macroadenoma in all subjects. The mean fasting at 2 hour post glucose load GH levels were 34.04±11.67 ng/ml and 36.47±6.64 ng/ml.

Eleven subjects (14.7%) were diagnosed to have prolactinomas. These included 9 females and 2

Table 1 - Clinical features and hormonal abnormalities in patients with somatotroph adenoma (N=44).

Characteristic	Values
Mean age (years)	41.23±11.78*
Gender	
Male	28
Female	16
Presentation	
Acromegalic features	44
Neurological manifestations	24/44
Cardiovascular abnormalities	18/44
Sexual disturbances	7/44
Diabetes mellitus	4/44
Impaired glucose tolerance	3/44
Growth hormone (ng/ml)	
Fasting	36.57±6.64*
Two hours post 100g oral glucose	34.04±11.67*
Associated pituitary dysfunction	
Hypothyroidism	13/44
Hypogonadism	12/44
Hyperprolactinemia	2/44
Hypocortisolism	10/44

*Mean±SD

males. **Table 2** describes the clinical presentation of subjects with prolactinoma. All females had amenorrhea and galactorrhea and one third had recurrent first trimester abortions. Both males presented with headache, visual symptoms and impotence. Both males had an enlarged sella whereas lateral sellar volume was normal in females. Microprolactinoma was detected in 7 females on contrast-enhanced computed tomography (CECT) scan and 2 females on MRI, whereas both the males had a macroadenoma documented on CECT. Twelve subjects were diagnosed to have non-functioning pituitary adenoma. Pituitary macroadenoma was detected on CECT in all these subjects. Their mean age at presentation was 40.75±14.60 years, which was slightly more for males (44.33±12.66 versus 30±17.35). **Table 2** also gives the clinical characteristics of these subjects. All these patients had presented with neurological symptoms. Most of the subjects would either get operated in the valley or outside, and postoperative follow-up was poor and available in only few patients. Cushing's disease was diagnosed in 8 subjects (6 females and 2 males). Pituitary microadenoma was detected on CECT in 5 patients where as in others contrast enhanced MRI documented microadenoma. Clinical and hormonal characteristics of these 8 patients are given in **Table 2**. Six underwent pituitary surgery and 2 underwent bilateral adrenalectomy. Two patients were confirmed to have periodic hormonogenesis.

Discussion. Prevalence of occult pituitary adenomas in unselected autopsies ranges from 11-23%,[5,6] while that of clinically overt tumors in the general population is estimated to range between 0.02-0.25%.[7] Our study revealed that somatotroph adenoma constituted more than half of the pituitary tumors (58.7%) followed by NFPT (16%), prolactinomas (14.7%) and corticotroph adenoma (10.7%). Prevalence of pituitary tumor in unselected surgical material reveals prolactin secreting adenomas to be the most common tumor followed in the decreasing order of frequency by NFPT, GH producing and corticotrophin producing tumor.[8] Our study being a retrospective analysis of data with its inherent limitations mainly consisting of patients who were evaluated at our endocrine services, it is possible that there may be a slight bias towards the functioning tumors. It is possible that subjects with prolactinomas could have more often been seen by a gynecologist for irregularities in menstrual cycles or infertility and those with NFPT would have straightway gone for surgery without prior endocrine evaluation. During the same period, we evaluated many patients for amenorrhea or galactorrhea with hyperprolactinemia who were taken care of in our outpatient clinic only and are therefore, not a part of this study. Earlier, we documented hyperprolactinemia as a cause of primary infertility in 8.4% of women evaluated at our center.[9]

The mean age at presentation in patients with somatotroph adenoma in our study was 41.23±11.78 years, which is in consensus with the literature.[8,10]

Table 2 - Clinical profile of prolactinoma, corticotroph adenoma and non-functioning pituitary adenoma.

Parameters	Prolactinoma N=11	Corticotroph adenoma N=8	Non-functioning pituitary adenoma (N=12)
Age (years), Mean±SEM	29.0±8.83	32.74±10.79	40.75±14.60
Gender			
Male	2	2	9
Female	9	6	3
Clinical presentation			
Amenorrhea/galactorrhea/infertility	9/11	0/8	0/12
Impotence	2/11	-	3/12
Neurological symptoms	6/11	-	12/12
Hormonal abnormalities			
Serum prolactin (>200 ng/ml)	11/11	-	-
Serum cortisol (µg/dl), Mean±SEM			
2mg dexamethasone suppression	-	16.40±4.52	-
8mg dexamethasone suppression	-	9.39±4.38	-
Associated hormonal dysfunction			
Hypothyroidism	2/11	0/8	2/12
Hypogonadism	7/11	0/8	3/12
Hypocortisolism	2/11	0/8	2/12
Hypersomatotropinemia	2/11	0/8	0/12

Our study revealed a male preponderance. Most of the previous studies have shown either an equal sex distribution or slight female preponderance.[8,10] Jamjoom et al[11] also reported a high proportion of males in the Kingdom of Saudi Arabia. The reasons for a female predominance could be due to poor medical care access by women than men. Frequency of symptoms and signs is almost consistent with the available published material. Two subjects presented before puberty and were primarily evaluated for tall stature. Somatotroph adenoma presenting as gigantism has been reported in <5% of the subjects.[12] Nine percent of the subjects had DM and were controlled on insulin or oral hypoglycemic agents; 6.8% of the subjects had impaired glucose tolerance. In the non-diabetic subjects, the mean of 2 hours post prandial venous plasma glucose was 156.90±41.19 mg/dl. The less frequency of DM in our study is not clear. All subjects were non-obese, none had a family history of DM or had an actively functioning somatotroph adenoma. Two patients had prolactin excess. All subjects had a macroadenoma and their mean lateral sellar volume was 183.9±53.18 [normal value <130 sq.mm].[2] Modi et al[13] found that growth hormone producing pituitary tumors are usually large in size and growth hormone levels correlate with the size of the tumor. One each of the patients with somatotroph adenoma developed colonic malignancy and chronic myeloid leukemia. None of our subjects had hypercalcemia, so further evaluation for a possible multiple endocrine neoplasia was not considered.

Hyperprolactinemia was diagnosed in 11 subjects (9 females and 2 males). Mean age at presentation was 29±8.83 years. Prolactinomas are relatively rare in males and more than 70% of the cases occur in females.[14,15] In our study, all women with prolactinomas presented with classical symptoms of amenorrhea-galactorrhea, and 33% females had recurrent first trimester abortions. Both males presented with headache, visual symptoms and impotence. Sellar enlargement on plain x-ray was seen in both the males and both had a macroadenoma. Women with hyperprolactinemia are usually detected early due to classical presentation of amenorrhea and galactorrhea and usually have a microadenoma. The presentation of prolactinoma in males is usually confusing;[16-18] impotence and decreased libido are the most frequent symptoms but the diagnosis is only made after the signs of compression due to tumor supervene.[19,20] Delay in seeking medical advice possibly explains the large size of tumors in men, however, more aggressive tumor behavior in men cannot be excluded.[21]

Non-functioning pituitary tumors do not produce any hormones but may cause a deficiency of one or more pituitary hormones by crowding out normal pituitary tissue or prolactin excess by causing stalk compression. Sixteen percent of our subjects were diagnosed to have NFPT. Approximately 25-30% of patients are described to have NFPT in the literature.[20] The lower percentage of NFPT in our series could be due to the fact that patients with NFPT may directly go for surgery without prior hormonal evaluation. In our series, NFPT was more common in males than in females with male to female ratio of 3:1. Most of the subjects presented with headache and visual symptoms and 2 had central hypothyroidism (**Table 2**), which is in agreement with the previous studies.[8] All the subjects had a sellar enlargement on plain x-ray which reflects the fact that tumor is invariably a macroadenoma.

Cushing's disease was diagnosed in 8 subjects (6 females and 2 males). It was confirmed by 2 and 8 mg dexamethasone suppression tests. All of them had a pituitary microadenoma on CT scan or MRI. The clinical details of these patients are already published.[22] Two subjects underwent bilateral adrenalectomy. One patient with pituitary microadenoma demonstrated on MRI continued to have features of hypercortisol state even after surgery. Six months later, the patient underwent right adrenalectomy and was planned for left adrenalectomy a month later. However, patient reported after 6 months with marked improvement in obesity, hypertension and DM. Endocrine evaluation revealed remission of Cushing's disease on follow up. Two years later she continues to have eucortisol state. We presumed a fluctuating hypercortisolemia in this as well as in one more patient on follow up. Fluctuating hypercortisolemia has previously been reported in some patients with Cushing's disease. These changes in cortisol dynamics are possibly due to unexplained erratic changes of ACTH secretion.[23]

The prevalence of occult pituitary adenomas in unselected autopsies is very high, while that of clinically overt tumors in the general population is very low. With the easy availability of sensitive imaging tools, the number of pituitary mass lesions diagnosed would be very high. Such "incidentalomas" need to be tackled judiciously, to avoid unnecessary pituitary surgeries. Same is not the case with functioning pituitary tumors, where hormonal disturbances would anyway require definite and specific management.

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