Study of management strategies in ACTH secreting pituitary microadenoma of Cushing’s disease

M.S. Senthil Kumar¹, Rajan Ganesan²*, A. Nithyanandham³, V. Kannan⁴, T. Suresh Babu⁵, K. Prabhakaran⁶

¹Assistant Professor, Department of Endocrine Surgery, Madras Medical College, Chennai, Tamil Nadu, India
²Professor, Department of Medicine, Stanley Medical College, Chennai, Tamil Nadu, India
³,⁴Assistant Professor, Department of Neurology, Madras Medical College, Chennai, Tamil Nadu, India
⁵Professor, Institute of Neurosurgery, Madras Medical College, Chennai, Tamil Nadu, India
⁶Formerly Professor and HOD, Department of Radiology, Madras Medical College, Chennai, Tamil Nadu, India
*Corresponding author email: medisen@gmail.com

Abstract

Background: Pituitary Microadenomas can be defined as small lesions less than 1 cm in the pituitary and detected as incidentalomas. Partial development or late development around puberty leads to maldevelopment of secondary sexual characteristics due to pituitary adenomas. Clinically this may manifest as secondary amenorrhea and may lead to hyperprolactinaemia, galactorrhoea and Amenorrhoea. ACTH secreting micro adenomas of the Pituitary Gland is a clinical entity where the role of surgery is contemplated. This study attempted to explore the management options and strategies for pituitary microadenomas.

The aim of the study: To highlight the characteristics of Cushing’s disease and discuss the management strategies including trans-sphenoidal surgery to treat ACTH secreting pituitary microadenomas.

Materials and methods: This was a non-randomised prospective observational study involving all adrenal tumors from 2007-2017 in Madras Medical College, Chennai. Two adrenocortical adenomas
with virilising features were ruled out and 8 ACTH secreting Cushing's disease with microadenomas were identified. 3 Patients with ACTH secreting microadenomas of Cushing's disease underwent surgery whereas 3 underwent medical treatment based on which this paper attempted to discuss management strategies for Cushing's disease.

**Results:** ACTH levels were measurable with an average of 136.71pg/ml (normal 7.2-63.3 pg/ml) Corticotrophin releasing hormone test was planned to evaluate an exaggerated response of serum cortisol consistent with pituitary disease. It was not carried out and inferior petrosal sampling also was not done. Biochemical evaluation confirmed pituitary dependent Cushing’s disease. MRI revealed a prominent circumscribed lesion suggestive of a Pituitary Micro Adenoma in All 6 Cases.

**Conclusion:** Pituitary micro adenomas are operable and in Cushing’s disease offer an effective cure. The outcome is good with minimal complications, but surgeons must have a thorough knowledge of the surrounding anatomy and potential complications.

**Key words**
Pituitary Microadenoma, Amenorrhoea, Cushing’s disease, Cushing’s syndrome, Transsphenoidal Surgery.

**Introduction**
Cushing disease is a condition in which the pituitary gland releases excessive adrenocorticotropic hormone (ACTH) as a result of an adenoma arising from the ACTH-secreting cells in the anterior pituitary [1]. ACTH secreting pituitary adenomas lead to hypercortisolemia and cause significant morbidity and mortality. Pituitary-directed medications are mostly ineffective, and new treatment options are needed. As these tumors express EGFR, we tested whether EGFR might provide a therapeutic target for Cushing disease. Here, we show that in surgically resected human and canine corticotroph cultured tumors, blocking EGFR suppressed the expression of proopiromelanocortin (POMC), the ACTH precursor [2]. In mouse corticotroph EGFR transfectants, ACTH secretion was enhanced, and EGF increased POMC promoter activity, an effect that was dependent on MAPK. Blocking EGFR activity with gefitinib, an EGFR tyrosine kinase inhibitor attenuated POMC expression, inhibited corticotroph tumor cell proliferation, and induced apoptosis [3]. As predominantly nuclear EGFR expression was observed in canine and human corticotroph tumors, we preferentially targeted EGFR to mouse corticotroph cell nuclei, which resulted in higher POMC expression and ACTH secretion, both of which were inhibited by gefitinib [4]. In athymic nude mice, EGFR overexpression enhanced the growth of explanted ACTH-secreting tumors and further elevated serum corticosterone levels. Gefitinib treatment decreased both tumor size and corticosterone levels; it also reversed signs of hypercortisolism, including elevated glucose levels and excess omental fat [5].

**Materials and methods**
This was a non-randomised prospective observational study involving all adrenal tumors from 2007-2017 in Madras Medical College, Chennai. Exclusion criteria were employed for all incidentalomas and inclusion criteria applicable for all adrenal tumors with clinical biochemical and imaging proven adrenal tumors. Accordingly, 390 adrenal lesions from 2007 until 2017 with a one year follow up was utilised in this study excluding all adrenal incidentalomas. After exclusion of 360 incidentalomas, biochemically and radiologically diagnosed 22 pheochromocytomas were excluded. 8 patients with typical cushingoid features were screened for hypercortisolism, overnight dexamethasone suppression test, ACTH and IGF-1, thyroid profile and hormone profile and other modalities. Two adrenocortical adenomas with virilising features were ruled out and 8 ACTH secreting Cushing’s disease with microadenomas were
identified. 3 Patients with ACTH secreting microadenomas of Cushing's disease underwent surgery whereas 3 underwent medical treatment based on which this paper attempted to discuss management strategies for Cushing’s disease.

**Technique**
The transsphenoidal procedure as used today was described and successfully performed almost a century ago by bold pioneer surgeons such as Cushing and Hirsch. All our patients were positioned supine and the throat packed with roller guaze tied to the endotracheal tube for removal post procedure. The pack prevents operative blood from draining into the stomach and causing postoperative nausea and vomiting. Endonasal Exposure is achieved by retracting the nostril with nasal speculum exposing the middle turbinate and the mucosa is detached from the bony posterior septum. The rostrum of the sphenoid and the sphenoid sinus ostia are an exposed. The anterior wall of the sphenoid sinus is opened widely. After the sphenoid sinus has been entered, the sella floor is usually easily identified as a recognizable convex surface. The floor of the sella is then opened and the dura is exposed once the dura has been exposed adequately, it is opened in a cruciate fashion and the tumour comes into view. The tumor was soft and sustainable, and removed with a ring curette with suction and an enucleator. The floor of the sella is reconstructed using either bone, cartilage. The sella can be packed with fat, especially if there is a cerebrospinal fluid leak which in our case was not necessary. Post-operative sequelae was the notable diuresis effect resulting in Urine output 10000 ml beyond first 5 days in 2 patients which settled with Vasopressin spray and after 5th POD onwards and in one patient the urine output was 5000 ml that further came down to 3000 ml on 7th post operative day. This indicated the completeness of microadenoma resection and attributed to resection to have supposedly encroached the posterior pituitary margin. Most pituitary adenomas were microadenomas and had an estimated prevalence of 16.7% (14.4% in autopsy studies and 22.5% in radiologic studies). In the diagnostic approach to a suspected pituitary adenoma, it is important to evaluate complete pituitary function, because hypopituitarism is common. Therapy for pituitary adenomas depends on the specific type of tumor and should be managed with a team approach to include endocrinology and neurosurgery when indicated. Dopamine agonists are the primary treatment for prolactinomas. Small nonfunctioning adenomas and prolactinomas in asymptomatic patients do not require immediate intervention and can be observed.

Clinical manifestations can be [4, 5, 6]

- Asymptomatic - does not cause mass effect
- Macroadenomas (Uncommon in Cushing’s disease)
- Mass effects when size exceeds 15 mm
- Suprasellar extension/ optic chiasma compression/ local bone erosion/ cavernous sinus compression
- Panhypopituitarism as macroadenoma enlarges.

**Results**
All 6 cushing's disease patients presented with Headache, Weight gain, Increased Blood Pressure unresponsive to antihypertensives and all 6 were in the Reproductive age group and had completed family with two children. Clinical examination revealed Striae on the arms and waist, acne, puffiness of face and meanblood pressure was 150/100 mm Hg. 3 patients with Cushing’s disease did not have truncal obesity. Cranial nerves were examined and found to be normal. 2 had facial hair but no evidence of virilisation or any other over stigmata of Cushing's syndrome. Mean Serum cortisol was 26.88 at 8 am estimation (normal 6.2-19.4 mcg/dl). A 1 mg overnight dexamethasone suppression test revealed a suppression of serum cortisol and low dose (0.5 mg four times a day) dexamethasone partially suppressed serum cortisol from 35.88 micrograms/dl to 28.43 microgram/dl (normal is 6.2-19.4 microgram/dl).
Serum cortisol was suppressed not fully though by high dose (2 mg 4 times a day) to an average of 23.96 mcg/dl. Serum Prolactin average was 14.04 ng/ml (normal 4.79-23.3 ng/ml). Plasma ACTH levels were measurable with an average of 136.71pg/ml (normal 7.2-63.3 pg/ml) Corticotrophin releasing hormone test was planned to evaluate an exaggerated response of serum cortisol consistent with pituitary disease but was not carried out and inferior petrosal sampling was not done. Biochemical evaluation confirmed pituitary dependent Cushing’s syndrome = Cushing’s disease. MRI revealed a prominent circumscribed lesion suggestive of a pituitary microadenoma in all 6 cases (Table – 1, 2, 3).

**Table – 1:** Adrenal tumors from radiological console (n=390).

<table>
<thead>
<tr>
<th>Incidentalomas</th>
<th>360</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pheochromocytomas</td>
<td>22</td>
</tr>
<tr>
<td>Adrenocortical carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Cushing’s disease (Medical Management)</td>
<td>3</td>
</tr>
<tr>
<td>Cushing’s disease (subjected to surgery)</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table - 2:** Clinical presentation in pituitary microadenomas.

<table>
<thead>
<tr>
<th>Clinical presentation in Pituitary Microadenomas</th>
<th>Pituitary Microadenomas 6 cases (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstrual irregularities</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Lactorrhoea,</td>
<td>2(6)</td>
</tr>
<tr>
<td>Amenorrhea,</td>
<td>2(6)</td>
</tr>
<tr>
<td>Delayed puberty,</td>
<td>2(6)</td>
</tr>
<tr>
<td>Maldevelopment of secondary sexual characteristics</td>
<td>3(6)</td>
</tr>
<tr>
<td>Hirsutism,</td>
<td>2(6)</td>
</tr>
<tr>
<td>Headache</td>
<td>5(6)</td>
</tr>
<tr>
<td>Visual disturbances</td>
<td>3(6)</td>
</tr>
</tbody>
</table>

**Table – 3:** Dexamethasone suppression.

<table>
<thead>
<tr>
<th>3 patients subjected to surgery</th>
<th>Serum Cortisol (6.2-19.4mcg/dl) Average</th>
<th>Plasma ACTH (7.2-63.3pg/ml) Average</th>
<th>Serum Prolactin (4.79-23.3) ng/ml Average</th>
<th>Electrolytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre op</td>
<td>35.88mcg/dl</td>
<td>96.71pg/ml</td>
<td>14.04 ng/ml</td>
<td>WNL</td>
</tr>
<tr>
<td>Low dose dexa suppression average</td>
<td>28.43mcg/dl</td>
<td>83.9471pg/ml</td>
<td>10.91 ng/ml</td>
<td>WNL</td>
</tr>
<tr>
<td>High dose dexa suppression average</td>
<td>23.96mcg/dl</td>
<td>89.61pg/ml</td>
<td>9.83 ng/ml</td>
<td>WNL</td>
</tr>
<tr>
<td>After surgery Average</td>
<td>3.38mcg/dl</td>
<td>1.97pg/ml</td>
<td>12.96ng/ml</td>
<td>WNL</td>
</tr>
</tbody>
</table>

**Discussion**

Cushing’s disease is responsible for roughly 2/3 of cases of endogenous Cushing’s syndrome and the remainder 1/3 is Ectopic ACTH secreting tumours and primary adrenal neoplasms [7]. Cushing’s disease is pituitary dependent with elevated ACTH levels whereas Cushing’s Syndrome-long term exposure to excessive glucocorticoids. Menstrual irregularities, galactorrhoea, amenorrhoea, delayed puberty, maldevelopment of secondary sexual characteristics, hirsutism, headache and visual disturbances are all associated with pituitary microadenomas. Clinical presentation includes Buffalo hump, Weight gain, Moon Facies, striae, Hypertension, Impaired GTT Usually
Microadenomas (by definition 10 mm or less) [8]. The diagnosis of Cushing’s disease is a vital part to establish the ACTH secreting micro adenoma with the aid of the response pattern to dexamethasone suppression test and the CT/MRI imaging patterns [9]. When it is confirmatory and the diagnosis is certain it is not mandatory to carry out petrosal sinus sampling which is recommended if there is uncertainty in diagnosis. Petrosal sinus sampling is helpful to confirm pituitary source of ACTH and lateralisation of adenoma. The option of surgery as the optimal therapy depends on individual patient and in these 3 patients the outcome of surgery had been favourable. Surgery for pituitary micro adenoma is generally not undertaken except for Cushing’s disease with ACTH secreting micro adenoma and hence this is highlighted. Medical management with ketocanazole 200 mg once daily dose for three weeks which was later withdrawn due to altered liver function test and raised bilirubin levels and unremitting headache [10]. Though cabergoline a potent dopamine receptor agonist can be used they were attributed to tumour shrinkage in residual tumours after surgery with a 8-45% success rate. Somatostation analogues on the other hand caused shrinkage of 5 -2.55 after one year of octreotide therapy. Temozolomide/tazeotride has been tried but not systematically studied. For prolactinomas, therapy with a dopaminergic drug is the treatment of choice (see Hyperprolactinemia). The most common are bromocriptine and cabergoline [11]. Cabergoline is the primary dopamine agonist used, or it is used if there is bromocriptine intolerance or resistance. Acromegaly may be medically controlled with long-acting somatostatin analogues, dopamine agonists such as cabergoline, or growth hormone receptor antagonists. For microadenomas, medical therapy is an alternative to surgical resection. Patients with apparent functional hyperprolactinemia may be harboring small pituitary adenomas. This possibility should be considered when using bromocriptine therapy. Pregnancy in patients with pituitary adenomas may be either normal or complicated by pituitary tumor enlargement, hemorrhage, or visual disturbances. There is no known accurate predictor of individual risk [12]. Patients conceiving spontaneously or after induced ovulation should be followed closely to detect and treat possible pituitary or visual complications, or both, as rapidly as possible, thereby avoiding serious permanent sequelae [13]. According to the endocrine society’s clinical guidelines and recommendations 3.0 states that the indications for surgical therapy includes: A VF deficit due to the lesion, Other visual abnormalities such as ophthalmoplegia or neurological compromise due to compression by the lesion, Lesion abutting or compressing the optic nerves or chiasma on MRI, Pituitary apoplexy with visual disturbance hypersecreting tumours other than prolactinomas as recommended by other guidelines of the endocrine society and pituitary society. Since the patient had unremitting headache and declining endocrine function, it was decided to undertake Transsphenoidal microadenomectomy with the aim to normalise hypothalamic-pituitary-adrenal function through the endonasal approach. Recently endoscope with inbuilt high powered microscope are available which improves cure rate to 87% from 76%. Sublabial approach is an alternate to endonasal route. Steroids were used as twice daily dose prior to surgery [14].

**Conclusion**

Pituitary micro adenomas are operable and in cushings disease - offers effective cure. The outcome is good with minimal complications, but surgeons must have a thorough knowledge of the surrounding anatomy and potential complications.

**References**


