Cushing’s syndrome – An update in diagnosis and management

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Abstract
Cushing’s syndrome results from chronic exposure to excess glucocorticoids and if remains undiagnosed/untreated is associated with increased morbidity and mortality. The classical clinical features of Cushing’s syndrome are not always present and a high index of suspicion is required in many cases. Furthermore Cushing’s syndrome should be differentiated from pseudo-Cushing’s syndrome seen in association with obesity, chronic alcoholism, depression and acute illness of any type. This review will highlight the clinical features, diagnostic approach, and current treatment strategies for timely diagnosis and treatment of Cushing’s syndrome.

Introduction
Cushing’s syndrome results from chronic exposure to excess glucocorticoids and if remains undiagnosed/untreated is associated with increased morbidity and mortality\textsuperscript{1,2}. It was first described by Harvey W Cushing in 1932. Iatrogenic Cushing’s syndrome resulting from long-term use of exogenous glucocorticoids is the most common cause of Cushing’s syndrome. Endogenous Cushing’s syndrome is broadly classified into ACTH-dependent and ACTH-independent, and is more common in women than in men\textsuperscript{3} (Table I). The term Cushing’s disease is reserved for pituitary dependent Cushing’s syndrome. ACTH-dependent Cushing’s syndrome includes Cushing’s disease, ectopic ACTH syndrome, and ectopic CRH syndrome. While ACTH-independent Cushing’s syndrome includes adrenal adenoma, adrenal carcinoma, primary pigmented nodular adrenal hyperplasia (Carney’s syndrome), macronodular adrenal hyperplasia, Mc-cune-Albright syndrome and aberrant receptor expression (gastric inhibitory polypeptide, interleukin-1B, leutensising hormone)\textsuperscript{4-7}. The incidence of pituitary-dependent Cushing’s syndrome is 5 to 10 cases per million population per year while that of ectopic ACTH syndrome parallels that of bronchogenic carcinoma. The common causes of ectopic ACTH syndrome include small cell lung carcinoma, carcinoids (pancreatic, bronchial, thymic), medullary carcinoma of thyroid, pheochromocytoma, and rarely carcinoma of the prostate, breast, ovary, gall bladder, and colon\textsuperscript{5}. Overall, ACTH-dependent causes account for 80 - 85% of cases and of these 80% are due to Cushing’s disease, and 20% are due to ectopic ACTH secretion and the rest are ACTH independent\textsuperscript{1}.

Table I: Cushing’s syndrome – aetiology.

<table>
<thead>
<tr>
<th>ACTH-dependent Cushing’s syndrome (80%)</th>
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<tbody>
<tr>
<td>1. Pituitary dependent Cushing’s syndrome: 68%</td>
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<tr>
<td>2. Ectopic ACTH syndrome: 12%</td>
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<td>3. Ectopic CRH syndrome: rare (&lt;1%)</td>
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<table>
<thead>
<tr>
<th>ACTH-independent Cushing’s syndrome (20%)</th>
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<tr>
<td>1. Adrenal adenoma: 10%</td>
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<td>2. Adrenal carcinoma: 8%</td>
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<td>3. Macronodular adrenal hyperplasia: rare (1%)</td>
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<td>4. Micronodular adrenal hyperplasia: rare (&lt;1%)</td>
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<tr>
<td>5. Aberrant receptor expression (gastric inhibitory polypeptide, interleukin-1B, leutensising hormone): rare (&lt;1%)</td>
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Clinical features
The classical clinical features of Cushing’s syndrome include centripetal obesity, moon faces, hirsutism, plethora, red-purple striae, bruising, proximal muscle weakness, psychiatric disturbances, osteoporosis, and menstrual irregularity\textsuperscript{3}. Glucocorticoid excess causes obesity by stimulating adipogenesis through transcriptional activation of adipocyte differentiation gene including lipoprotein lipase, glucorol-3-phosphate dehydrogenase and leptin. Furthermore, excess glucocorticoid by reducing CRH (which normally has anorexic effect) causes increase in appetite and weight gain. The most discriminatory features that help in distinguishing Cushing’s syndrome from simple obesity include signs and symptoms of protein catabolism, i.e., proximal muscle weakness, red-purple striae, bruising, cuticular/pulp atrophy and osteoporosis. However, these gross clinical symptoms and signs are not always present and a high index of suspicion is required in many cases. Glucose intolerance and overt diabetes mellitus is seen in up to one-third of cases. Glucocorticoid increases hepatic glucose output by activation of key gluconeogenesis enzyme...
phosphoenolpyruvate carboxykinase. Hypertension is seen in up to 75% of cases by increasing cardiac output, activation of rennin-angiotensin system by increasing hepatic production of angiotensinogen, decreasing synthesis of vasodilatory nitric oxide, enhancing the pressor sensitivity to endogenous catecholamines and by specificity spillover with activity on mineralocorticoid receptors. There is 2 - 5% prevalence of unsuspected Cushing syndrome in patients with poorly controlled diabetes mellitus14-16, 3% in patients with osteoporosis17, and 9% among patients with incidental adrenal mass of more than 2 cm18. Since clinical features of polycystic ovary syndrome overlap with those of Cushing's syndrome, it should be ruled out in such patients19. Less common and unappreciated clinical features of Cushing's syndrome includes exophthalmos, chemosis, lisch nodule and central serous chorioretinopathy20-22. Clinical features like cataract, increased intraocular pressure, benign intracranial hypertension, aseptic necrosis of femoral head, osteoporosis, and pancreatitis are more common in iatrogenic Cushing's syndrome; whereas hypertension, hirsutism, and oligomenorrhoea are rare.

In children, adrenal causes account for 65% of all cases with Cushing's syndrome17. The growth retardation, obesity and delayed puberty is the most common presenting feature18. However, adrenal androgen excess usually seen in patients with adrenocortical carcinoma may result in precocious pseudopuberty. Muscle weakness is less common reflecting the effect of growing age. Depression is less common than adults and these children may show compulsive diligence – and actually do quite well academically.

Thus, it requires a high index of clinical suspicion for making an early diagnosis of Cushing's syndrome and it should be ruled out in patients with symptoms/signs/clinical diagnosis as summarised in Table II.

### Table II: Screening of Cushing's syndrome.

<table>
<thead>
<tr>
<th>1. Central obesity with features of protein catabolism</th>
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<tbody>
<tr>
<td>Facial plethora</td>
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<tr>
<td>Cuticular atrophy</td>
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<tr>
<td>Cutaneous wasting with bruise and ecchymosis</td>
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<tr>
<td>Wide violaceous striae (&gt;1cm)</td>
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<tr>
<td>Proximal myopathy</td>
</tr>
<tr>
<td>2. Short stature with obesity and delayed bone age</td>
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<tr>
<td>3. Metabolic syndrome (2 - 5%)</td>
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<tr>
<td>Uncontrolled diabetes</td>
</tr>
<tr>
<td>Resistant hypertension</td>
</tr>
<tr>
<td>Polycystic ovary syndrome</td>
</tr>
<tr>
<td>4. Osteoporosis at young age (3%) especially with rib fracture</td>
</tr>
<tr>
<td>Premenopausal women</td>
</tr>
<tr>
<td>Men &lt; 65 years</td>
</tr>
<tr>
<td>5. Incidental adrenal mass &gt; 2 cm (9%)</td>
</tr>
<tr>
<td>6. Hypogonadotropic hypogonadism with increased lanugo hair and papular acne</td>
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### Diagnosis

Cushing's syndrome should be differentiated from pseudo-Cushing's syndrome4. Pseudo-Cushing's is defined as a state in which some or all the clinical features that resemble Cushing's syndrome and evidence of hypercortisolism are present on screening test, but disappear after resolution of underlying condition. The most common causes of pseudo-Cushing's syndrome include obesity, chronic alcoholism, depression and acute illness of any type. The tests used to differentiate between these two clinical disorders are insulin tolerance test, loperamide (16 mg orally) test and combined dexamethasone-CRH test. Out of these three tests, combined dexamethasone-CRH test has sensitivity and specificity of 99% and 96% respectively. The test involves administration of 0.5 mg oral dexamethasone every 6 hour for 2 days, ending 2 hours before administration of ovine CRH (1mg/kg) intravenously. The plasma cortisol value 15 minutes after CRH less than 40 nmol/l (1.4 mg/dL) excludes the diagnosis of Cushing's syndrome45.

The diagnosis of Cushing's syndrome involves two steps. First, establishing that the patient is having hypercortisolaemia; and second, establishing the cause of this hypercortisolaemia. No single test is perfect and each has a different sensitivity and specificity. The tests used to establish a diagnosis of Cushing's syndrome include circadian rhythm of cortisol, urinary free cortisol (UFC), overnight and low-dose dexamethasone suppression test (ONDST and LDDST)26,27. In normal subjects, plasma cortisol levels are highest in the morning and reach a nadir (< 50 nmol/L) at about midnight. This circadian rhythm is lost in patients with Cushing's syndrome. The midnight cortisol > 200 nmol/L indicates Cushing's syndrome with sensitivity of 94% and specificity of 100%22,23. Since more than 90% of the plasma cortisol is protein bound, the results of conventional assay are affected by drugs or conditions that alter cortisol binding globulin (CBG). Midnight salivary cortisol represents free cortisol and is an alternative in such cases. It has a sensitivity of 93% and specificity of 100%. The normal value of salivary cortisol is 43 nmol/L, while patients with Cushing's syndrome had >8.6 nmol/L24. Patients with intermediate values should have a repeat measurement or should undergo UFC or LDDST. UFC values of more than four times the upper limit of normal are rare except in Cushing's syndrome. UFC has a sensitivity and specificity of 95 - 100% and 90 - 95% respectively. The overnight dexamethasone suppression test with 1 mg of dexamethasone given at 11pm in the night with 08 00 hr cortisol value of < 140 nmol/L has a sensitivity of 95% and specificity of 88%. The sensitivity of this test can be improved to 98 - 100% by reducing post-dexamethasone cortisol value to less than 50 nmol/
The 48-hour LDDST (0.5 mg dexamethasone every 6 hrs) with post-LDDST cortisol level of less than 50 nmol/L has a sensitivity of 98 - 100% and a specificity of 97 - 100%26. However, some 3% - 8% of patients especially those with cyclic Cushing's disease retain sensitivity to dexamethasone and show suppression of serum cortisol to less than 50 nmol/L on either test. Thus, if clinical suspicion remains high, repeated testing is indicated with future follow-up.

Having established the diagnosis of Cushing's syndrome, the next step involves finding out the cause of Cushing's syndrome. Measurement of 9 am ACTH differentiates between ACTH-dependent Cushing's syndrome from ACTH-independent causes. ACTH > 20 pg/ml suggests ACTH-dependent causes, while < 10 pg/ml suggests ACTH-independent aetiologies. Patients with values between 10 - 20 pg/ml should be subjected to CRH stimulation test (1 mg/kg IV). Post-CRH stimulation ACTH of more than 20 pg/ml suggests ACTH-dependent Cushing's syndrome27. The value of high-dose dexamethasone suppression test (HDDST) in discriminating various aetiologies is questioned by many studies28. There is a little difference between results of HDDST in patients with Cushing's disease and those with ectopic ACTH syndrome. Furthermore, if suppression of serum cortisol by more than 30% occurs with LDDST, there is no further advantage of using HDDST (Table III).

### Table III: Sensitivity and specificity of various biochemical tests used in making a diagnosis of Cushing's syndrome.

<table>
<thead>
<tr>
<th>Biochemical test</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>Loss of circadian rhythm with midnight cortisol &gt; 200 nmol/l</td>
<td>94%</td>
<td>100%</td>
</tr>
<tr>
<td>Overnight dexamethasone suppression test (ONDST) with a cutoff ≤ 50 nmol/l</td>
<td>98 - 100%</td>
<td>88%</td>
</tr>
<tr>
<td>Low dose dexamethasone suppression test (LDDST)</td>
<td>98 - 100%</td>
<td>97 - 100%</td>
</tr>
<tr>
<td>Late night salivary cortisol</td>
<td>93%</td>
<td>100%</td>
</tr>
<tr>
<td>High dose dexamethasone suppression test (HDDST)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* &gt; 90% suppression of basal 08 00 hr plasma cortisol</td>
<td>67 - 70%</td>
<td>100%</td>
</tr>
<tr>
<td>* 8 mg single dose</td>
<td>92%</td>
<td>100%</td>
</tr>
<tr>
<td>HDDST + CRH</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>Inferior petrosal sinus sampling (IPSS)</td>
<td>95 - 99%</td>
<td>100%</td>
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The algorithm for the diagnosis of Cushing's syndrome is shown in Figure 1.

**Fig. 1: Algorithm for the diagnosis of Cushing's syndrome.**

The next step involves MRI of sella if patient is suspected having pituitary-dependent Cushing's syndrome, or CT scan of the chest and abdomen to find out ectopic source of Cushing's syndrome, or for adrenal causes of Cushing's syndrome. A major drawback of pituitary imaging is that up to 40% of cases with biochemically proven Cushing's disease have normal pituitary MRI scan and a tumour of less than 5 mm on imaging has a poor correlation with aetiological diagnosis29. In these cases inferior petrosal sinus sampling (IPSS) remains the gold standard. A basal central: peripheral ratio of more than 2:1 or 3:1 after CRH stimulation has a sensitivity of 95 - 99% and specificity of 100% in establishing a diagnosis of Cushing's disease30. The algorithm for the diagnosis of Cushing's syndrome is shown in Figure 1.

### Treatment

The patients with marked hypercortisolaemia, i.e., plasma cortisol > 1,200 nmol/l are especially at risk of severe infections like *Pneumocystis carinii*, aspergillosis, candidiasis, nocardiosis, cryptococcosis, and visceral perforation31. The approach of many centres to use routine pre-operative medical adrenal blockade with ketoconazole to achieve eucortisolaemia for 4 - 6 weeks.
before surgery to restore metabolic and catabolic effects of hypercortisolaemia is empirical. There is no randomised trial to support this approach. Since Cushing’s syndrome is a prothrombotic state, anticoagulant prophylaxis should be given to all the patient’s pre-operatively.

The treatment of Cushing’s disease is trans-sphenoidal surgery by an experienced neurosurgeon. Cure rate for microadenoma is 80 - 90% while it is only 50% for macroadenoma. The recurrence rate for established cure after successful pituitary surgery is 2% but this is higher in children (up to 40%). The undetectable cortisol within 24 - 72 hours after the surgery establishes the cure. Patients who are hypocortisolic (undetectable plasma cortisol) post-operatively should be given 10 mg/m² of hydrocortisone in three divided doses. Patients should be educated about the need to double the oral dose for nausea, diarrhoea, and fever, and should take intravenous glucocorticoid during severe medical stress. Recovery of HPA axis is monitored by measuring 9 am cortisol 24-hr after omission of hydrocortisone replacement. Because recovery of HPA axis rarely occurs before 3 - 6 months, it is cost-effective to do an initial testing at 6-months post-operatively. If the patient continues to show subnormal cortisol response up to 2 years after the surgery, then patient needs lifelong glucocorticoid replacement therapy. The adrenal adenoma should be removed by unilateral adrenalectomy with 100% cure rate. Adenoma of less than 6 cm size can be removed by laparoscopic adrenalectomy. Patient needs to be given hydrocortisone replacement therapy as trans-sphenoidal surgery. After unilateral adrenalectomy, the time to recovery of HPA axis may be as short as 3 months to as long as 2 years. Adrenal carcinoma has a poor prognosis as majority has metastasis at the time of diagnosis. Furthermore, adrenocortical carcinoma responds poorly to radiotherapy and chemotherapy.

Pituitary irradiation – both conventional or gamma knife – has been recommended to treat Cushing’s disease when surgery fails, except in children where pituitary irradiation is more effective and can be used as primary treatment modality for Cushing’s disease. The gamma knife has a remission rate of 76% with normalisation of cortisol value within 12 - 36 months.

Bilateral adrenalectomy provides rapid resolution of hypercortisolic state in any ACTH-dependent hypercortisolaemia; however, the patient needs to take lifelong glucocorticoid and mineralocorticoid replacement therapy. A major concern after bilateral adrenalectomy in patients with Cushing’s disease is the development of Nelson’s syndrome – a locally aggressive pituitary tumour that secretes high concentrations of corticotrophin, resulting in pigmentation. The exact pathogenesis of Nelson’s syndrome is not clear. It is believed that the tumour results either from the lack of cortisol feedback after adrenalectomy, or because of progression of previously undetected corticotrophine tumours that were programmed to behave in an aggressive manner from the beginning. The treatment of Nelson’s syndrome involves trans-sphenoidal pituitary surgery or radiotherapy. Some clinicians advocate use of prophylactic pituitary radiotherapy at the time of bilateral adrenalectomy to reduce the risk of this syndrome, but others have not confirmed this finding.

In Cushing’s disease, patients who fail to achieve a cure with TSS and or radiotherapy, or who cannot opt for adrenalectomy, medical therapy can be used to ameliorate hypercortisolism. Overall, medical treatment may be useful in up to one-third of Cushing’s disease patients. These agents fall under three major categories based on their mechanism of action, which include inhibitors of steroidogenesis, modulators of ACTH release, and cortisol receptor antagonists. Pharmacological management of Cushing’s disease is usually directed at decreasing adrenal steroid production by ketoconazole, mitotane, metapyrone, aminoglutethimide.

Ketoconazole is the best tolerated drug available for control of hypercortisolism. It is an imidazole derivative and inhibits 11-β hydroxylase, 17-hydroxylase and CYP 17 - 20 lyase enzyme activity. It also interferes with ACTH-induced cAMP production and is a weak competitor for glucocorticoid receptor. It is used in the dose of 200 - 400 mg twice or thrice daily and is effective in 30 - 50% of cases. It has been used safely up to 83 months in various studies. The oral absorption is facilitated by gastric acidity so it should be given after the meals, and concomitant use of antacids, proton pump blockers should be avoided. It can be used safely in children and in pregnant women. However, it is associated with hepatotoxicity in 5 - 10% of cases and causes gynaecomastia, oligozoospermia, and decreased libido in men.

Mitotane is a O,P'-DDT derivative and inhibits cholesterol side chain, 11-β hydroxylase and 3β-hydroxysteroid dehydrogenase enzyme. It spares aldosterone metabolism. It is effective in up to 80% of patients and its effect persists as long as 2 years even after stopping the drug due to its lipophilic properties. Its effect is seen at a dose of 4 - 12 gm once a day that achieves a plasma concentration of 14 - 20 µg/ml. However, a majority of patients develop neurological (drowsiness, gait disturbances, vertigo, and problem with language) and gastrointestinal (nausea, vomiting, and diarrhoea) side effects at this dose. These side effects can be avoided by beginning at a dose of 0.5 - 1 g/day, gradually increasing
at 1 - 4 week interval and by administering it with meals or at bedtime with milk. Other adverse effects include fatigue (due to decreased cortisol), gynaecomastia, hypouricaemia, hypercholesterolaemia, elevated liver enzymes, and abnormal platelet functions. Since mitotane increases cortisol binding globulin, sex hormone binding globulin and thyroxine binding globulin, total serum cortisol cannot be used to monitor therapy, and urinary free cortisol and/or ACTH should be used for this purpose. Also, it increases the metabolic clearance of exogenously administered steroid, so the replacement doses of glucocorticoid must be increased by approximately one-third.

In severely ill patient who are unresponsive or unable to ingest an oral drug, etomidate (an imidazole derivative) can be used intravenously at a dose of 1.2 - 2.5 mg/hr to control hypercortisolemia46. It has potent inhibitory effect on 11-β hydroxylase and less pronounced effect on 17-hydroxylase, 17-20 lyase and side chain cleavage enzyme activity. It also inhibits adrenocortical cell proliferation and expression of ACTH receptor. However, its use is limited because of its need to be given intravenously, and sedation which it causes even at therapeutic doses. After its use, adrenal insufficiency occurs invariably, therefore replacement with hydrocortisone or dexamethasone is mandatory.

Neuromodulatory compounds that affect CRH or ACTH synthesis or release include serotonin antagonists (cyproheptadine), dopamine agonists (bromocriptine and cabergoline), γ-amino butyric acid reuptake inhibitor (sodium valporate) and somatostatin analogue (octreotide). All these compounds are used principally for Cushing’s disease; however no large-scale placebo-controlled studies have been done with these compounds. A recent study demonstrated that dopamine receptors are expressed in neuroendocrine tumours associated with ectopic ACTH secretion causing Cushing’s syndrome. Cabergoline treatment was found to be associated with normalisation of urinary cortisol in a subgroup (66.7%) of these patients. However, studies involving larger number of patients are mandatory to confirm the usefulness of dopamine agonist in ectopic ACTH syndrome47-49.

Mifepristone (RU 486) is a competitive antagonist of glucocorticoid and progesterone receptors50. It is used in doses of 5 - 25 mg/kg or 400 - 800 mg/day. However, absence of peripheral marker of anti-glucocorticoid activity, long half-life, and difficulty in counteracting its anti-glucocorticoid activity limits the clinical use of this compound.

Newer medical treatment modalities include new multiligand somatostatin analogue SOM 230 (pasireotide), high-dose peroxisomal proliferator-activated receptor γ agonist rosiglitazone, retinoic acid, doxazosin51.

SOM-230 (pariseotide) has high affinity for somatostatin receptor subtypes sst1, sst2, and sst5 (respectively 30, 5 and 40 times more than octreotide) and has been recently studied in vitro52. Basal and corticotrophin-releasing hormone induced ACTH release was inhibited and sensitivity of this treatment was not influenced by pre-treatment with dexamethasone. The inhibitory effect on basal ACTH was seen only after prolonged exposure, and is probably due to resistance to desensitisation and/or downregulation of endogenously expressed sst5 receptors. In a recent study, expression of somatostatin receptor 1, 2, 4 and 5 have been demonstrated in 13 patients with Cushing’s disease and SOM 230 had been found to suppress cell proliferation and ACTH secretion in primary culture of human corticotroph tumours significantly53. These results suggest that SOM-230 may have a role in medical treatment of pituitary-dependent Cushing’s syndrome and multicentre clinical trials are underway to answer some of these questions.

Peroxisome proliferator-activated receptor expression is restricted and only colocalises with ACTH-secreting cells. There is abundant expression in ACTH-secreting adenomas. In vitro and in mice, plasma ACTH is significantly decreased by PPAR-γ ligands. As PPAR-γ ligands inhibit tumour cell growth in human breast cancer cells in vitro and in prostate cancer, it was postulated that it would have favourable effects on treating pituitary adenomas54. Rosiglitazone has been shown to induce G0/G1 cell-cycle arrest and apoptosis and suppress ACTH secretion in human and murine corticotroph tumour cells. Unfortunately, rosiglitazone is unable to affect ACTH and cortisol secretion, at least in acute conditions, in patients with ACTH-secreting pituitary adenomas. In a recent study (10 patients that underwent unsuccessful TSS and four that were untreated), the administration of a single dose of rosiglitazone did not decrease ACTH/cortisol levels or blunt their response after corticotroph releasing hormone injection55. In another study, seven patients with persistent Cushing’s disease after failed pituitary TSS were treated with rosiglitazone at a dose of 8 mg/day56. Three of the cases showed a mild clinical improvement, moderate ACTH response and marked decrease in urinary free cortisol levels for 1 - 4 months after initiation of treatment. In tumours that were removed from patients treated with rosiglitazone, about 50% of cells maintained strong ACTH immunoreactivity. It is not clear why PPAR-γ agonists have a more pronounced effect on cortisol secretion than on ACTH secretion; some studies postulate that these agents have a direct effect on steroidogenic
enzymes and on antagonism of the actions of glucocorticoids on target organs. In a recent study involving six patients with Nelson’s syndrome (bilateral adrenalectomy done for Cushing’s syndrome), rosiglitazone at a dose of 12 mg/day did not change circulating ACTH concentration over 12-week study period despite demonstration of PPAR-γ receptor expression in tumour tissue. However, the authors concluded that despite being a negative study the demonstration of PPAR-γ receptor over tumour tissue suggest that a higher dose or more potent agonist might prove useful in other patients.

Retinoic acid has been found to have a potent inhibitory effect on corticotrope tumour growth, plasma ACTH and corticosterone secretion, and reversed Cushing’s phenotypic characteristics in various animal models. This effect seems to be mediated through inhibition of the transcriptional activity of AP-1 and the orphan nuclear receptors Nur77 and Nur1. Retinoic acid treatment resulted in reduced pro-opiomelanocortin transcription and ACTH production. ACTH inhibition was also observed in human pituitary ACTH-secreting tumour cells, but not in normal cells, being correlated with the expression of the orphan receptor COUP-TFI (found in normal corticotrophes, but absent in pituitary Cushing’s tumours). These potential anti-secretory and anti-proliferative properties of this agent in Cushing’s syndrome need to be investigated further.

α1-adrenergic receptor antagonists also represent a potential novel therapy for pituitary adenomas. A study published in 2005 showed that doxazosin treatment inhibited proliferation of murine pituitary tumour cells and induced G0/G1 cell-cycle arrest. In mice with corticotrope tumours, doxazosin administration decreased tumour growth and reduced plasma ACTH levels. The mechanism is still unclear, but these effects were not mediated via the α1-adrenergic receptors. The validity of these observations needs confirmation in clinical trials.

Following successful treatment, features of Cushing’s syndrome disappear over a period of 2 - 12 months period. Skin desquamation occurs shortly after surgery and weight loss, decrease in medication for blood pressure and diabetes occurs over the time, and some may have normal glucose tolerance. Osteopenia improves slowly over 2 years; reproductive and sexual functions return to normal within 6 months. Vertebral fracture, aseptic necrosis are irreversible.

Thus, the diagnosis and treatment of Cushing’s syndrome remains a challenging problem in clinical practice with rewarding results if done timely.

References


