**Case Report**

**Cushing’s Disease: Establishing the Diagnosis and Management Approach**

Lakshminarayanan Varadhan*, Amit Arora**, Adrian B Walker***, George Iype Varughese**

**Abstract**

A 64 year old lady, with a background history of type 2 diabetes mellitus and hypertension, presented with general deterioration of general health, poor glycaemic control, difficulty in controlling blood pressure and difficulty in walking. She had past medical history of adenocarcinoma of the oesophagus, treated with surgery and subsequent chemotherapy. General examination revealed high blood glucose and blood pressure and a Cushingoid facies. Overnight dexamethasone suppression test and urinary free cortisol levels confirmed Cushing’s syndrome and High dose dexamethasone suppression test showed partial suppression. CT scan of the abdomen showed bilateral hyperplasia of the adrenals with nodularity on the left side, raising the possibility of an adrenal adenoma. ACTH levels were elevated thereby ruling out autonomously functioning adrenal nodule, however increasing the possibility of ectopic ACTH secretion due to the previous medical history. MRI of the pituitary confirmed the presence of an adenoma, thereby pointing to the diagnosis of pituitary dependant Cushing’s disease.

The patient could not undergo further invasive investigation or surgery due to septicaemia. Medical management of Cushing’s syndrome was resorted to in the interim with Ketoconazole, showing excellent response. This case depicts the need for a high index of suspicion for the diagnosis, the importance of organizing specific investigations in the appropriate order to arrive at a diagnosis and an effective management plan.

**Case Report**

A 64 year old lady with longstanding type 2 diabetes mellitus (DM) and hypertension was admitted to hospital with gradual deterioration of general health, easy bruising, very poor glycaemic control, high blood pressure and increasing weakness on walking warranting assistance with a frame. She also had history of adenocarcinoma of the oesophagus, treated with surgery and chemotherapy five years before this presentation. She was taking Simvastatin, Ramipril, Amlodipine, Furosemide, Omeprazole, Aspirin and a biphasic insulin (approximately 70units daily in divided doses) adjusted according to home glucose monitoring. She did not smoke or drink any alcohol.

On examination she was obese, with cushingoid facies, multiple bruises all over and hirsutism. Heart rate was 100/minute and regular and blood pressure 178/100mmHg. Respiratory, cardiovascular and abdominal examination was normal. Neurological examination revealed proximal muscle weakness with no evidence of arthritis.

Initial tests showed - Sodium 132mmol/L (135-145mmol/L), Potassium 2.9mmol/L (3.8-5.3mmol/L), Urea 7.7mmol/L (3.3-7.8mmol/L) and Creatinine 73µmol/L (55-108µmol/L). Haemoglobin was 11g/dl (13-18g/dl) with a normal white blood cell count. The liver function tests were deranged with alkaline phosphatase 153u/L (30-120u/L), alanine transaminase 65u/L (0-40u/L), gamma glutamyl transferase 948u/L (0-50u/L), total albumin 31g/L (35-50g/L) and total bilirubin 9µmol/L (0-17µmol/L). Blood glucose levels on the ward were always recorded ‘high’, requiring increasing doses of insulin. The results of random cortisol levels, dexamethasone suppression tests and urine free cortisol values are shown in Table 1.

A computed tomography scan of the chest and abdomen (Figure 1), which was initially done to rule out recurrence or

Table 1: Results of Cortisol and ACTH levels

<table>
<thead>
<tr>
<th>Endocrine Test</th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random Cortisol (nmol/L)</td>
<td>979</td>
<td>&gt;1380</td>
<td></td>
</tr>
<tr>
<td>Urine Free Cortisol (nmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Dose Dexamethasone Suppression (LDDST)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Cortisol (nmol/L)</td>
<td>&gt;2000</td>
<td>&gt;2000</td>
<td></td>
</tr>
<tr>
<td>Repeat LDDST – Serum Cortisol (nmol/L)</td>
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<td></td>
<td></td>
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<tr>
<td>High Dose Dexamethasone Suppression (HDDST)</td>
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<td></td>
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</tr>
<tr>
<td>Serum Cortisol (nmol/L)</td>
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<td>812</td>
<td></td>
</tr>
<tr>
<td>Urine Free Cortisol (nmol/L)</td>
<td>853</td>
<td>719</td>
<td>418</td>
</tr>
<tr>
<td>Urine Free Cortisol (nmol/day)</td>
<td>958</td>
<td>1198</td>
<td>532</td>
</tr>
<tr>
<td>ACTH (pg/ml) Reference range (&lt;46pg/ml)</td>
<td>131</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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metastatic disease from the previous oesophageal carcinoma, demonstrated bulky right adrenal gland, and slightly enlarged left adrenal gland with two small round nodules, consistent with either bilateral adrenal hyperplasia, left sided adenoma or metastatic lesion.

Magnetic resonance imaging (MRI) scan of the brain (Figure 2) demonstrated 7mmX8mm pituitary adenoma. Static pituitary profile of blood tests were normal [TSH 0.15mu/L (0.3-5.0mu/L), T4 15pmol/L (8-19pmol/L), Prolactin 214 mu/L (60-380mu/L), Serum Osmolality 281mOsmol/Kg (285-295mOsmol/Kg), Urine Osmolality 338mOsmol/Kg, FSH 2.2iu/L (1-8iu/L), LH 0.2iu/L (1-8iu/L), GH 0.3mIU/L (3.6-5.0mIU/L)]. During hospital stay, she developed an ulcer of the left elbow infected with Staphylococcus aureus and urinary tract infection with Pseudomonas, followed by septicemia. These infections were treated appropriately, but were followed by Clostridium difficile diarrhea, making her unfit for surgery. The patient eventually died secondary to septicemia.

**Differential Diagnosis and management approach**

The main differential diagnoses in this patient were:

a. Pituitary dependant Cushing’s disease (CD)
b. Cushing’s syndrome due to ectopic ACTH secretion (EAS)
c. Autonomous adrenal adenoma

The highly elevated urinary free cortisol (UFC) values and lack of suppression on the LDDST and overnight dexamethasone suppression test confirmed the diagnosis of Cushing’s syndrome and rules out a metastatic lesion causing hypoadrenalism. Elevated ACTH levels rules out an autonomous adrenal nodule thereby suggesting the CT scan report to be more consistent with bilateral nodular hyperplasia. The moderate suppression on HDDST, confounded with the presence of pituitary adenoma on MRI, and the inappropriately low pituitary gonadotrophins for post-menopausal women favours the diagnosis of pituitary dependant Cushing’s disease in 98-99% of the patients, though 10% of the patients in this age group could have a true pituitary incidentaloma.1

As this patient was unfit for surgery, medical management had to be used in the interim. Ketoconazole was initiated at a dose of 200mg qds, which was titrated down based on clinical response. Ketoconazole produced a dramatic response with quick and persistent drop in blood pressure and blood glucose within a week of initiation of therapy, forcing withdrawal of insulin treatment and a few antihypertensive drugs. Repeat UFC, on Ketoconazole, were remarkably better at 124nmol/d and 39nmol/d on two separate occasions. Hydrocortisone supplementation had to be started on a “block and replace” regimen basis, to ensure adequate steroid levels till surgery.

**Discussion**

Chronic glucocorticoid excess causes Cushing’s syndrome (CS), the most common cause being Cushing’s disease (CD) due to excessive ACTH from the pituitary gland (70%). The other most common reasons are ectopic ACTH secretion (EAS) (15-20%) and primary adrenal tumours (10%). The diagnostic assessment should aim to establish CS and then to differentiate its causation. Pseudo Cushing’s (presence of hypercortisolism without actual Cushing’s syndrome) could be present in alcoholism, depression, pregnancy and poorly controlled diabetes.

UFC, LDDST and midnight salivary cortisol are the initial investigations to demonstrate CS, with combined Dexamethasone Suppression-Corticotrophin releasing hormone stimulation test (DST-CRH) and circadian rhythm of cortisol secretion serving as second line investigations to establish CS.2 The cause of CS could then be differentiated using serum ACTH, HDDST, CRH stimulation test, pituitary MRI and bilateral inferior petrosal sinus sampling (BIPSS).3,4

UFC is useful screening test as this is not influenced by factors affecting cortisol binding globulin (CBG). Ideally three 24hour samples would be required to exclude intermittent hypercortisolism, and false positives could occur in pseudo-Cushing’s states (depression, pregnancy, alcoholism). LDDST is an easier and realistic method of screening for CS; done either by administering 0.5mg of Dexamethasone four times a day for two days or 1mg overnight. This test is however dependant on absorption and metabolism kinetics of Dexamethasone and also lacks specificity as complete suppression of endogenous steroid axis could be achieved in cyclical or mild CS.5,6 Loss of circadian rhythm on midnight salivary cortisol would be an easier screening tool and this in combination with UFC could serve as the ideal non-invasive screening test with high sensitivity.7 In our patient the diagnosis of CS was well established by high UFC and unsuppressed LDDST.

Once the diagnosis of CS is established, ACTH measurements could reasonably stratify the cause, with measurable levels of ACTH excluding autonomous adrenal adenoma. Though a very high level of ACTH is consistent with EAS, a slightly elevated ACTH level may not help to differentiate between ectopic and pituitary dependant CS.4 HDDST then helps to differentiate CD from EAS and could be done either by administering 2mg of Dexamethasone every 6 hourly for 2 days or 8mg of Dexamethasone overnight. The test is based on the principle that pituitary dependant CD still retains the responsiveness to negative feedback with high doses of steroid.4 The specificity of the test is around 60%, when 50% suppression of cortisol is used as an end point; this could be improved to 80% if 80% suppression is used. Of note, 20-30% of the ectopic ACTH may show suppression of >50% from baseline and 20-30% of the CD may not demonstrate adequate suppression. Dexamethasone suppression test (with 2mg/d for 48hrs) followed by CRH stimulation could also be used to differentiate between CD and EAS (sensitivity 98%, specificity 93%).8 In our patient, the significantly high ACTH rules out adrenal adenoma and the partial suppression points towards pituitary dependant CD.

A pituitary MRI, preferably with Gadolinium contrast, would pick up an adenoma in 60% of the cases with CD and an
unequivocally proven CS with an adenoma >6mm is consistent with CD. Bilateral petrosal sinus sampling (BIPSS) with CRH stimulation would be the more reliable diagnostic test for CD, especially if the MRI does not demonstrate an adenoma. Petroal sinus ACTH to peripheral ACTH ratio of greater than 2 in the unstimulated state and ratio greater than 3 after CRH stimulation supports diagnosis of CD. Surgery remains the cornerstone of treatment, with transphenoidal microsurgery for selective adenomectomy being the first choice and partial or total hypophysectomy being an alternative with higher risk of hypopituitarism or inadequate remission. Conventional radiotherapy in patients with recurrent or persistent disease after surgery and bilateral adrenalectomy with the future risk of Nelson’s syndrome are other treatment options. The medical management of CS aims at adrenal directed inhibition of steroidogenesis, two commonly used drugs being Ketoconazole and Metyrapone. Ketoconazole is an ideal option in patients with persistent hypercortisolism after surgery or CS of unknown aetiology or in patients needing long term suppression of hypercortisolism. However, close monitoring of liver function and monitoring for hypogonadism in men, are essential. Metyrapone is an ideal alternative with potent blocking effect on aldosterone synthesis, causing accumulation of 11-deoxycorticosterone, which may cause hypokalaemia, oedema and hypertension. As our patient remained unfit for surgery, medical management was opted. The coexistence of illnesses such as hospital acquired infection could have contributed to inappropriately low levels of some of her pituitary hormones. However during times of severe infections, the need for steroid response to combat illness was recognised and hence was supplemented alongside Ketoconazole in a ‘block and replace’ regimen of management.

Conclusion

The variable pattern of biochemical parameters and rather nonspecific symptoms pose a common clinical challenge. The specificity, or rather the lack of it, makes it a huge challenge to diagnose Cushing’s syndrome and the causation of it. It is therefore pertinent that hypercortisolism is unequivocally established before proceeding to more complicated biochemical and radiological investigations.

References