CASE REPORT

A CASE OF CUSHING SYNDROME OF UNDETERMINED CAUSE MANAGED MEDICALLY WITH CABERGOLINE

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Abstract

We report a 77 year old lady with hypertension and hypokalaemic metabolic alkalosis who was found to have ACTH dependant Cushing Syndrome (CS). Cortisol level was not suppressed during low dose as well as high dose dexamethazone suppression test (HDDST). Her pituitary MRI was normal and inferior petrosal sinus sampling was consistent with ectopic ACTH secretion. CECT of the abdomen and chest was normal. She was started on medical treatment with a plan of re-imaging during the follow-up. As she couldn’t tolerate ketoconazole and since our options were limited, she was started on Cabergoline to which she has shown a good response until the time of this report. Cabergoline has been reported to show varying efficacy according to the available literature. This report highlights the efficacy of cabergoline in this selected case of CS.

Keywords: Cushings syndrome

Background

Cushing syndrome (CS) is a constellation of signs and symptoms resulting from supra-physiological cortisol levels. It is associated with increased morbidity and mortality even when treated, since the treatment is usually not straight forward. Investigations showed hypokalaemia with metabolic alkalosis. She was referred to the Endocrinology Unit for further management. Examination showed her to be overweight (BMI 24.8 kg/m²). She was clinically not Cushingoid but had significant generalized hyperpigmentation (Figure-1).

Case report

A 77-year-old female patient was investigated in a medical ward for non-specific symptoms such as body aches and malaise. She had high blood pressure and biochemical investigations (table 1) revealed spontaneous hypokalaemia with non-suppressed O DST, LDDST and HDDST and inappropriately normal ACTH levels confirming ACTH dependant CS.
Table: Results of laboratory investigations

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>3.2mmol/L</td>
<td>3.5-5.0</td>
</tr>
<tr>
<td>Overnight Dexamethazone Suppression Test</td>
<td>39.7µg/dL=1095nmol/L</td>
<td>&lt;1.8µg/dL or &lt;50nmol/L</td>
</tr>
<tr>
<td>Low dose Dexamethazone Suppression Test</td>
<td>27.4µg/dL=755nmol/L</td>
<td>&lt;1.8µg/dL or &lt;50nmol/L</td>
</tr>
<tr>
<td>Repeat LDDST</td>
<td>29.9µg/dL=824nmol/L.</td>
<td>&lt;1.8µg/dL or &lt;50nmol/L</td>
</tr>
<tr>
<td>High dose Dexamethazone Suppression (HDDST)</td>
<td>Base line - 29.9 µg/dL</td>
<td>≥50% suppression from basal value</td>
</tr>
<tr>
<td></td>
<td>Day 3 – 29.2 µg/dL</td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>39.4pg/mL</td>
<td>9-69 pg/mL</td>
</tr>
</tbody>
</table>

Discussion

In this patient with ACTH dependant CS, pituitary MRI, HDDST and IPSS were concordant in suggesting an ectopic ACTH secretion. Therefore, the diagnosis in this case vignette remains as 'ectopic ACTH syndrome of undetermined cause'. Endogenous CS in itself is an uncommon disorder. Ectopic ACTH syndrome is responsible for 15% of CS and represents 20% of ACTH dependant CS. Many neuroendocrine and other tumours can be associated with ectopic ACTH syndrome.

Brain MRI with dynamic studies did not show any pituitary lesions. Inferior petrosal sinus sampling (IPSS) was consistent with ectopic ACTH secretion. Contrast enhanced CT of the chest and abdomen was negative for culprit lesions.

Since the investigations did not reveal the cause for the ‘inappropriate ACTH secretion’, it was decided to treat the patient medically, while following up the patient with serial imaging to detect the lesion as early as possible. The patient was started on Ketoconazole but she developed troublesome nausea and vomiting. Then she was switched over to Cabergoline to which the patient showed good clinical and biochemical response. Currently the patient is being closely followed up for dose adequacy, drug side effects and any new evidence of the primary lesion.

Untreated CS results in complications such as cardiovascular complications, infections and psychiatric illness leading to increased morbidity and mortality. In one study, the median survival of uncured CS was 4.6 years, and 5-yr survival was about 50%, with most deaths caused by vascular (myocardial infarctions, cerebrovascular accidents) or infectious complications.

Diagnosis as well as management of patients with CS can be very challenging. Once a diagnosis of ACTH-dependant CS is made, it’s of utmost importance to exclude with confidence the possibility of Cushing disease, before considering an ectopic ACTH syndrome. There is a 90% probability of Cushing disease when a woman has an ACTH-dependant CS. Out of confirmed Cushing disease patients,
40% have normal pituitary MRI\(^3\). Thus, unless there is a clear extra-pituitary lesion, the usefulness and the necessity of an experienced interventional radiology team to perform IPSS cannot be overemphasized.

Several options are available in view of finding a lesion responsible for ectopic ACTH secretion, but one should be mindful of the possibility of detecting an incidentaloma that is not responsible for the ACTH secretion, especially in patients who are older than 40 years. CT and/or MRI of neck, thorax, abdomen and pelvis are often the initial imaging techniques used. Given the fact that neuroendocrine tumours are the commonest cause for ectopic ACTH secretion and that they can be small tumours, somatostatin receptor scintigraphy may be of use to disclose the lesion. Other options include \(^{11}\text{C}\)-5-hydroxytryptophan with PET and \(^{68}\text{Ga}\)-octreotate PET scanning. Despite all these investigations, 5-15% of cases will remain ‘occult’. Therefore, while biochemically controlling the ‘cushing’ status, long term follow up is necessary to detect the causative lesion by regularly repeating one or more of the above tests.

A good response to Cabergoline in our patient can be due to a ‘cyclical’ CS as well. This is frequently associated with ACTH secreting pituitary adenomas but there are a few reported cases of ectopic secretion\(^4\), thus only time will tell whether it is the diagnosis in this patient since ‘cycles’ can last for few hours to years.

References


