Cushing's syndrome. *Case illustration and guidelines in management*

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The patient is a 43-year-old housewife, with a history of gaining weight over the last 19 years, in addition to type 2 diabetes mellitus (DM) and hypertension over the past 9 years. Blood glucose was increasingly uncontrolled, eventually requiring insulin treatment. Physical examination showed a depressed lady with truncal obesity (103 kg), supraclavicular fat padding and abdominal striae.

Low dose dexamethasone suppression test (LDDST) was positive for Cushing's syndrome (CS) with a plasma cortisol of 31.4μg /dl (normal < 1.8 μg /dl). Baseline cortisol level was greater than 50 μg/dl and adrenocorticotropin hormone (ACTH) 44 pg/ml (both are high) indicating ACTH dependent Cushing's disease (CD). For localization of ACTH production, high dose dexamethasone suppression test (HDDST) was carried out and cortisol level decreased to 6 μg/dl (more than 80% reduction) suggesting pituitary ACTH production. Magnetic resonance imaging (MRI) of the pituitary gland was non-conclusive as far as demonstrating pathology (**Figure 1a & 1b**). Inferior petrosal sinus sampling was thus, conducted to confirm the diagnosis of CD and try to lateralize the side of ACTH secretion. It was suggestive of a left-sided pituitary adenoma (**Table 1**).

The patient underwent sub-labial transsphenoidal pituitary surgery, where a left-sided adenoma was found and resected, with an uneventful postoperative course. Eight-am serum cortisol level on the 3rd postoperative day, was less than 1 μg/dl. A month after the surgery the patient's mood was very good, and she had lost 6 kg with a fasting blood glucose of 120 mg/dl off insulin. The serum ACTH level was less than 10, indicating cure after holding prednisone for 2 days.

Management of Cushing's Syndrome. Clinical suspicion is still the corner stone in detecting suspected cases of CS.[1] The decision of further investigating the patient, depends on how high the suspicion is; especially that several disorders can raise the cortisol level, in addition to the possibility of having false negative results in episodic and intermittent CS variant. Endogenous CS is caused by excess glucocorticoids production due to increased ACTH secretion in 80-85% of the cases, or less frequently due to primary adrenal disease.[1] Detailed history including intake of oral, inhaled, or topical steroids, and history of weight gain and associated diseases is an integral part of assessment, in addition to thorough physical examination looking for abdominal obesity, supraclavicular fat pad and purple striae.[1]

Does the patient have CS? Overnight 1 mg dexamethasone is a simple inexpensive screening test, taking into consideration that the normal level was lowered from 5 μg/dl to 1.8 μg/dl. Lowering the normal value, increased the sensitivity, allowing detection of mild cases at the expense of specificity.[2] Pseudo-Cushing's, medical illness, or abnormalities in cortisol binding globulin (CBG) might test positive.[2,3] Twenty-four-hour urinary cortisol is both a screening and confirmatory test. It measures free (unbound) cortisol, so it is not affected by CBG abnormalities.[2] Up to 3 urine collections may be performed, as some patients have intermittent hypercortisolism state.[1] Urine volume and kidney functions are major determinants, so urine creatinine should be requested in all collections. Late-night salivary cortisol is a useful test and correlates with free plasma cortisol. The test is conducted in limited centers, and the normal values are not standardized.[3] Elevated midnight plasma cortisol (over 1.8 μg/dl) is a very sensitive test but lacks specificity, which can be as high as 100% if the value went up to 7.5 μg/dl.[3] Low-dose dexamethasone suppression test is the classical test, with a sensitivity of 79% and specificity of 74% only. Both can be enhanced to more than 95%, if plasma cortisol was measured instead of urinary cortisol, with cut off at 1.8 μg/dl.[2] The combined dexamethasone suppression test (DST) and corticotropin-releasing hormone (CRH) test is a highly sensitive and specific confirmatory test for CS. Dexamethasone is given orally, and a plasma cortisol value greater than 1.4 μg/dl 15 minutes after intravenous CRH is diagnostic for CS.[2,3]

Where is the problem? The next step in the cascade of investigating CS patients is localization of the abnormality. Plasma ACTH level at 9 am distinguishes between ACTH-dependent and adrenal CS. In the former, serum ACTH concentration is greater than 20 pg/ml, while in the latter, ACTH is suppressed to less than 10 pg/ml. Values between 10-20 pg/dl require CRH stimulation test.[1]

At this point, the patient is classified to either ACTH independent CS, which needs further work up by adrenal computed tomography (CT) scan or preferably MRI, or ACTH-dependent requiring further localization to differentiate between a pituitary source, or CD and ectopic ACTH sources. High dose dexamethasone suppression test helps to identify a pituitary adenoma, as it mainly suppresses pituitary corticotrophs but not ectopic ACTH

production, although some well differentiated neuroendocrine tumors can be suppressed. Different versions of this test are mentioned in the literature; the simplest is the overnight test. Cortisol suppression to more than 50% of the baseline is considered positive. Though this test has high specificity, it lacks high sensitivity (60 - 80%).[4] In the CRH stimulation test, administration of CRH will increase plasma ACTH and cortisol levels in case of pituitary adenoma, but not ectopic ACTH-producing tumors, though they may also respond. The test is considered positive if there is an increase in ACTH by 35 - 50% and in cortisol by 14 - 20%. The desmopressin acetate (DDAVP) test is not very specific, but can be used however, in postoperative evaluation.

Bilateral inferior petrosal sinus sampling (BIPSS) is the simultaneous measurement of ACTH from both inferior petrosal sinuses (IPS) and peripheral blood (P). It is the most sensitive, most specific, and most accurate test in distinction between pituitary and ectopic ACTH production. Furthermore, lateralization of the lesion is possible, especially when the pituitary MRI is inconclusive. Both IPS are catheterized, and blood samples for ACTH are obtained at baseline, then 3, 5, and 10 minutes after injecting 1 μg/kg CRH. An IPS to P ACTH ratio (IPS/P) greater than 2 in the basal state or greater than 3 after CRH or both are an indication of a pituitary adenoma, while a lower ratio is consistent with an ectopic ACTH producing tumor. Lateralization is suggested if the interpetrosal ratio is greater than 1.4.[5] Pituitary MRI with gadolinium enhancement should be performed in all ACTH-dependent CS. Unfortunately, only 35 - 60% of ACTH secreting adenomas will be revealed.[3]

Hypercorticolism is associated with hypertension, DM, dyslipidemia, cardiomyopathy, and coagulopathy, which cause the CS patient to have 4 folds the mortality when compared to the general population.[6] The 5-year survival rate of untreated CS is only 50%.[6] Depression, vertebral fractures due to osteoporosis, and growth suppression in pediatric population is also common. Thus, CS mandates urgent treatment to reduce the mortality and morbidity.

The first line of treatment of CD, which is the main cause of CS, is transsphenoidal adenomectomy with exploration of contra lateral side if the tumor is not encountered. If the tumor is not identified, hemihypophysectomy of the side suggested by IPSS is carried out, with the consent of the patient. Transsphenoidal surgery is effective and safe in the adult and pediatric population, though the result is center-dependent, and remission rates are reported to range between 0% to above 90%.[7] Generally, the cure rate for microadenoma is 80 - 90%, and for macroadenoma 50% and up to 67% in one series.[7]

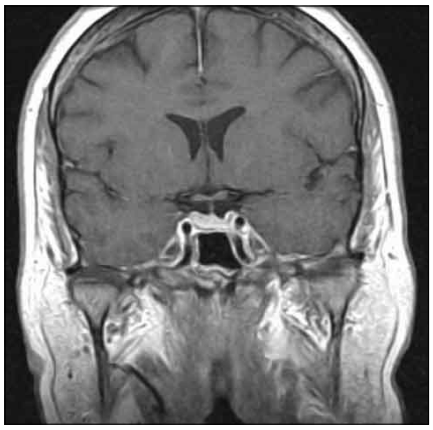

Figure 1a - Coronal T1-W images after gadolinium administration, at the level of the pituitary. Although a left sided pituitary adenoma may be visualized in retrospect, the images were not confirmatory of the presence of an adenoma.

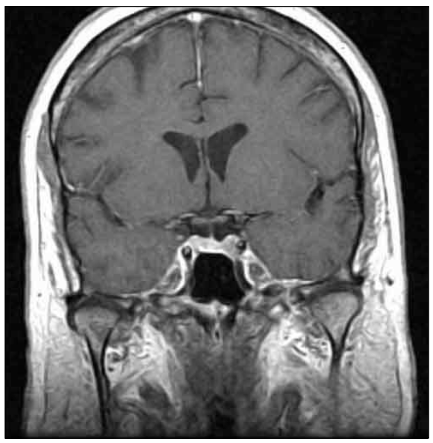

Figure 1b - Postoperative coronal T1-W images after gadolinium administration demonstrating resection of the pituitary adenoma.

Table 1 - Inferior petrosal sinus sampling of ACTH after injection of 1 μg/kg of CRH.

ACTH pg/ml (minutes)	Left IPS	Right IPS	Peripheral
- 5	206	29	19.9
0	310	51	35
5	774	323	165
10	693	597	265

ACTH - adrenocorticotropin hormone, CRH - corticotropin-releasing hormone, IPS - inferior perrosal sinuses.

Large tumor size and cavernous sinus invasion are the main predictors of residual disease in macroadenoma.

Indicators of cure are morning cortisol levels less than 1.8 g/dl, measured in the first 2 weeks after surgery after holding hydrocortisone for 24 hours (also predictive of lower probability of recurrence). Negative desmopressin test in the postoperative period is also considered a good cure indicator. Other predictors of long-term remission are the absence of cortisol response to CRH, and the need for long-term glucocorticoid substitution therapy.[8] In persistent CD, early re-operation may be performed, with higher incidence of hypopituitarism. The pituitary hormonal work up should take place 6 weeks after any pituitary surgery. Patients are maintained on hydrocortisone replacement postoperatively, and tapered according to the clinical status. Periodic cosyntropin stimulation test may help to identify full adrenal recovery.

In conclusion, patients with CS have higher mortality and morbidity. The presentation of the syndrome is variable, and a high clinical index of suspicion is a main tool in diagnosis. Probable CS cases should undergo a battery of investigations for screening, confirmation and localization of the source. Lateralization of the pituitary adenoma by petrosal sinus sampling is helpful in order to perform resection with higher chance of success. Abolishing hypercortisolism decreases mortality and reverses most of the CS complications. Expert endocrinologists, radiologists and neurosurgeons are required to work together to obtain the best possible results.

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