A clinical syndrome resulting from chronic glucocorticoid excess is called Cushing’s syndrome (CS), named after Harvey Cushing who first described the same. The clinical syndrome can be due to Endogenous or Exogenous (chronic steroid ingestion) causes. The Endogenous CS can either be ACTH dependant or ACTH independent. ACTH dependant CS is due to pituitary hyper secretion [Cushing’s disease (CD) 80- 90% of all CS] of ACTH (hyperplasia or tumor) or ACTH from an ectopic site (secondary to malignant disease producing ACTH) ACTH independent CS is the result of adrenal disorders (tumors and bilateral adrenal nodular hyperplasia: 10- 15% of all CS). After nearly a century of its first description, it has remained one of the most enigmatic disease to diagnose and treat. Exogenous CS is usually due to chronic steroid administration for definite indications like nephrotic syndrome, SLE and other autoimmune disorders. Occasionally it is due to self administration by the patient as with patients of bronchial asthma. A detailed history usually elicits chronic intake of drugs and a basal cortisol of undetectable or <5µg/dl is sufficient to confirm exogenous CS. This is the commonest cause seen in clinical practice.

Diagnosis and Management of Endogenous Hypercortisolemia: (See Table 1)
The clinical features are weight gain manifesting as central obesity, menstrual irregularities or amenorrhea, purple striae of the skin, acne, hirsutism, proximal muscle weakness and some times associated with hypertension and diabetes. Presence of acanthosis nigricans and hyperpigmentation is suggestive of ACTH dependant CS. Children may present with simple obesity, growth retardation or rarely precocity. CS can be rarely cyclical and if such a history is obtained, patient should be investigated during an active cycle.

Screening Tests
The screening tests are done to confirm or rule out endogenous hypercortisolemia, which is the first step in the investigation of CS.

1. Overnight Dexamethasone Suppression Test (ODST)
   Basal normal or elevated cortisol is not sufficient to rule out or confirm CS. The simple screening
test on out patient basis is ODST. The principle of the test is to suppress the pituitary ACTH secretion by dexamethasone and estimating the cortisol secretion at 8 am, usually the peak period. The test is performed by giving 1 mg dexamethasone at 11pm and estimating plasma cortisol at 8 am on the following morning. Lack of suppression to <1.8µg/dl is considered suggestive of CS and requires further evaluation. The sensitivity and specificity is around 95%. Stress, alcoholism, severe obesity and endogenous depression can give a false positive result.

2. 24 hour Urinary cortisol (UFC):
Normal 24 hour urinary cortisol is 100-120 µg/ day. Values above 200 µg are diagnostic of CS. In addition to collection problems, it has high sensitivity, but has poor specificity; requiring multiple UFC for diagnosis. Hence it is not in common use.

3. Low Dose Dexamethasone Suppression Test (LDDST)
This test is performed by giving 0.5 mg dexamethasone 6 hourly for 48 hours and collecting plasma cortisol 8 hours after last dose. A plasma cortisol value < 1.8 µg/dl rules out CS. The specificity is 97 –100%. Though originally, a urinary hydrocortisone was estimated in the classical test, it is more convenient without loss of sensitivity and specificity to use plasma cortisol. UFC can also be estimated over the 24 hours and in normal people, it is usually <10 µg/dl. Again...
urine collection is cumbersome as compared to single blood collection. Several modifications have been described, but the above test is simplest to perform.

4. Midnight Plasma Cortisol and ACTH
The early morning values of plasma cortisol can be normal in some cases of CS, but the circadian rhythm is lost in all. Hence a midnight cortisol value of >1.8µg/dl is suggestive of CS. A cut off value of > 7.5µg/dl has been used by some to distinguish from pseudo-Cushing state. We prefer the former cut off value. The test requires admission to the hospital for 2 nights, the collection being made on the second night within 5-10 minutes of waking the patient. A simultaneous ACTH may offer valuable additional information and will be discussed later. The sensitivity of the test is reported to be 100%.

Late night salivary cortisol estimation is a relatively new addition as a screening test and has the advantage over other tests in terms of simplicity of collection and not requiring hospital administration. However, due to technical difficulties and non availability of assay kits, this is not a feasible alternative in our country at present.

Differentiating between ACTH dependent vs. ACTH independent CS

Determination of ACTH
Once endogenous hypercortisolemia is established, the next step is to determine if cortisol secretion is dependent or independent of ACTH. The ACTH value will be suppressed if cortisol is secreted independently of ACTH as in adrenal lesions. ACTH collected during the midnight can be processed at this time, though most of the literature uses 8 am collections. We use this as midnight levels as it reduces one needle prick and secondly, should if at all be lower than the morning cortisol in normal people.

An ACTH level of <5pg/ml is suggestive of ACTH independent CS - suggestive of an adrenal disease – adenoma or nodular hyperplasia and an adrenal imaging should be done to confirm the diagnosis. Occasionally such a level is seen in CD especially if RIA is used. Hence it is recommended that IRMA ACTH be done.

An ACTH level of >10 pg/ml is suggestive of ACTH dependent disease – pituitary or ectopic production.

Localization of site of ACTH secretion (DD of ACTH dependent CS)

ACTH level
To differentiate between CD (pituitary ACTH secreting lesion) vs. ectopic ACTH secretion usually from a carcinoid (bronchial, thymes or other malignant tumors), the level of ACTH may be helpful. In Cushing’s disease, the hypothalamo pituitary axis is set at a higher level and hence ACTH will be normal or slightly elevated - >10pg/ml, but usually <100pg/ml. In ectopic ACTH secretion as in malignancy, the ACTH level can be very high (>200pg/ml). However, there is a lot of overlap and distinction of Cushing’s disease vs. that of ectopic ACTH production is not always possible.

High Dose dexamethasone Suppression Test
The basis of this test is that in CD, the pituitary has a high set, but normal hypothalamo-pituitary-adrenal axis. High doses of steroid does suppress the pituitary resulting in decreased ACTH and consequently the cortisol secretion, whereas an ectopic ACTH secreting tumor is basically autonomously functioning and cannot be suppressed. Though this presumption is true most of times, bronchial (or other) carcinoid tumors at early stages similar to pituitary and long standing pituitary tumors may not show suppression.

The test is performed by giving dexamethasone 2mg 6 hourly (8mg HDDST) starting at 8 am for 2
days and estimating plasma cortisol 8 hours (8 am on the second day) after the last dose at 2 am. If this does not suppress, the test can be performed with double the dose of dexamethasone (16 mg HDDST). ≥50% suppression from the basal level is considered positive and suggestive of CD. A lesser suppression or lack of suppression is expected with ectopic Cushing’s Syndrome as well as ACTH independent lesions (in adrenal lesions, this test was used before the availability of ACTH estimation). The test can be simplified by doing an overnight 8 mg or 16 mg HDDST, where the dose of dexamethasone is given at 11 pm and cortisol estimated in the 8 am sample next day. Other modification of the test such as IV dexamethasone has been tried to improve the sensitivity and specificity.

To be foolproof, the sensitivity and specificity of the test should be better than the pre test probability of the diagnosis. The pre test probability of CD is almost 85 – 90% in any given case of CS. Hence, the sensitivity (57 – 92%) and specificity (57-100%) of HDDST is often insufficient for a clear discrimination and there is a chance of false positive or false negative test to the tune of 10 – 15%. However, the test is useful as an additional pointer in the diagnostic work up. Many of us have stopped doing the test routinely.

CRH stimulation test also has been used to differentiate CD (responds to CRF) from adrenal lesions, but as it is not available in India easily and has not proved superiority over other tests in solving diagnostic difficulties, it is mainly used for research purposes.

**Imaging**

Instead of HDDST, a pituitary MRI could be done. A tumor seen is diagnostic of CD along with ACTH level. Tumors less than 4mm requires ruling out a pituitary incidentaloma and hence may require further evaluation. Also, normal pituitary imaging does not rule out CD. In these situations, imaging of the thorax and abdomen is needed to look for ectopic lesions. Presence of bilateral adrenal hyperplasia points towards an ACTH dependant disease. An ectopic lesion may not be visualized if very small (especially bronchial adenoma or carcinoma) and further testing would be required.

**Inferior Petrosal Sinus Sampling (IPSS)**

This test is done to confirm or rule out pituitary as the site of ACTH secretion when the pituitary imaging is negative, there is bilateral adrenal hyperplasia and there is no visualization of ectopic tumor.

A catheter is introduced into both inferior petrosal sinuses. ACTH is estimated in the samples collected from both these sites and from the peripheral vein either basally or preferably after CRH stimulation. A ratio of periphery: petrosal sinus = 1:2 at basal collection or =1:3 after CRH is diagnostic of pituitary ACTH secretion. Absence of a gradient is typically found in ectopic ACTH secretion. The test has a sensitivity of 96% and specificity of almost 100% when CRH stimulated values are used; and lesser when only basal values are used. However, the test is invasive and should be done by centers with necessary skills to avoid complications such as hemorrhage. The CRH availability is a problem in our country, so also the cost involved. It is necessary to understand that in normal individuals, there would be a peripheral to petrosal sinus ratio of 1:2 at the basal state and hence establishing endogenous hypercortisolism is a pre requisite for the test.

Once localized, surgery should be performed, depending on the site of lesion. What should be done if at the end of all tests, ACTH secretion cannot be localized? This is a dilemma for the endocrinologist and as excessive cortisol secretion leads to increased morbidity and mortality, choice is between a Transsphenoidal exploration (an experienced surgeon can identify tumors not seen on imaging) and removal of tumor if found or a bilateral adrenalectomy. If the latter mode is used, patient should be followed up for signs of pituitary or ectopic ACTH secreting tumor on a regular basis.

There are several newer tests described as well as several modifications of the older tests. It is not possible to discuss all of them and I have discussed the most useful and time tested ones in this article.
Suggested Further Reading:


2. The Diagnosis and Differential Diagnosis of Cushing’s Syndrome and Pseudo-Cushing’s States. John Newell-Price, Peter Trainer, Michael Besser and Ashley Grossman. Endocrine Reviews 19 (5): 647-672