Cushing’s Disease: Management Outcome in a Tertiary Care Centre

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Abstract
Cushing’s syndrome (CS) can pose a challenge in diagnosis and management. Successful management of CS needs accurate localization of the site of lesion. Present article narrates experience of a single center dealing with large number of patients with CS and highlights difficulties in diagnosis as well as management of Cushing’s disease (CD).

Methods: All patients with CD, where histopathological lesion was documented were studied to evaluate yield from different diagnostic tests. Diagnosis was established by standard 2 days low dose dexamethasone suppression test. Localization of the lesion was achieved with high dose dexamethasone suppression (HDDS) and imaging. Inferior petrosal sinus sampling (IPSS) was used whenever diagnosis was not arrived at with the standard tests.

Results: Out of 100 consecutive patients of CS seen, 69 had CD. HDDS had sensitivity of 70% and specificity of 99% in localizing the lesion. Imaging localized the lesion in 68% of patients. Combination of HDDS and imaging localized the lesion in 90% of patients. IPSS helped to localise the lesion in remaining 10% of patients.

Transsphenoidal surgery was carried out in 65/69 patients. Cure rate for microadenoma was 77% and for macroadenoma was 36%. Mortality and morbidity rate was 7% and 7% respectively. 2nd TSS, radiotherapy and bilateral adrenalectomy were the additional modalities used in that order, in patients who were not cured or who had recurrence.

Conclusion: Management of CS is best carried in a center where a team of experienced endocrinologist and neurosurgeon is available.

INTRODUCTION
The key to success in management of Cushing’s syndrome (CS) rests on localization of source of endogenous hypercortisolism. Several tests are available for diagnosis and localisation of endogenous hypercortisolism. It requires an experienced physician to opt for appropriate tests and interpret them correctly for final diagnosis, along with a good laboratory back up. In the present article, it is proposed to discuss accuracy rate of various diagnostic tests that are used at our center and narrate outcome of our patients with Cushing’s disease (CD).

MATERIAL AND METHODS
All the diagnostic tests were validated against histopathological outcome. More than 100 patients were referred to our center for management of CS in the past 16 years of which 69 were CD. Diagnosis of endogenous hypercortisolism was based on standard low dose dexamethasone suppression test (LDDS, post LDDS serum cortisol > 5 µg/dl) (Cortisol estimation performed by Diagnostic System Laboratories, intra assay cv : 5.3 to 11.1%, inter assay cv : 8.9 to 11.5%). After LDDS, all patients were subjected to overnight high dose dexamethasone suppression test (HDDS) of 8 mg, 16 mg and 32 mg on three consecutive days. Suppression of ≥ 50% over the basal value with any of the high dose dexamethasone suppression tests was taken as an indicator of Cushing’s disease (CD).

Patients with a strong clinical and/or biochemical suspicion of adrenal carcinoma or ectopic ACTH secreting tumors were subjected to CT scan of abdomen and chest respectively, which proved the diagnosis. All the remaining patients were subjected to imaging of pituitary, preferably MRI, depending on the cost and availability of the same. Patients with negative pituitary imaging were subjected to imaging of abdomen and chest. Positive finding on any of these imaging was then
dealt with appropriately.

Patients where tumor was not localised on imaging (pituitary, abdomen, chest), were subjected to inferior petrosal sinus sampling (IPSS) irrespective of degree of suppression on HDDS. Ratio of central to peripheral ACTH value of ≥2 was taken as suggestive of CD. In patients with ratio of <2 and negative imaging, repeat clinical and biochemical evaluation was carried out after a period of observation to discern the cause of CS.

Patients with CD were subjected to trans sphenoidal surgery (TSS) when 2 out of 3 tests (HDDS, imaging, IPSS) were pointing towards pituitary. In patients who had strong clinical and biochemical suggestion of CD, TSS was carried out even with 1 positive test, provided adrenal carcinoma and ectopic ACTH secreting tumors were excluded on the basis of imaging.

Post-op cure rate was defined as basal serum cortisol value of <5 μg/dl, which was generally done between 5th to 7th postoperative day.

RESULTS

Diagnostic distribution of 100 patients seen with proven endogenous hypercortisolism is as shown in Table 1. There was a clear preponderance of females in general and CD was the commonest problem encountered. In 13 patients diagnosis could not be achieved due to lack of follow up.

HDDS

HDDS was not done in 3/69 patients (2 patients were referred for not having been cured after first surgery done outside for further management and 1 patient had 17 KGS done on HDDS) of CD and they are not included in analysis for HDDS.

HDDS showed suppression in 46/66 (70%) patients. (Sensitivity 70%, specificity 99%). One patient with ectopic ACTH secreting tumor showed suppression on HDDS. In 28 patients of CD where 8 mg of dexamethasone did not show suppression, 8 patients achieved suppression with 16 mg but none showed suppression with 32 mg of dexamethasone.

Imaging

In CD, imaging was positive in 46 out of 68 (68%) patients. (32 microadenomas, 14 macroadenomas, 7 doubtful, 13 normal, and 1 empty sella syndrome: sensitivity 68%, specificity 100%) One patient died before imaging could be done due to left ventricular failure (LVF). Her final diagnosis was achieved on post-mortem. 16 out of 46 patients with CD with ≥50% suppression on HDDS did not show tumor on imaging. Out of 20 patients who did not show suppression on HDDS, imaging proved the diagnosis in 16 patients (11 microadenoma, 5 macroadenoma, 4 no tumor) leaving 4 patients of CD in diagnostic difficulty where both HDDS and CT were negative.

IPSS

IPSS was carried out in 39 patients with cannulation rate of 100%. 21 out of 32 patients with CD had ratio of ≥2. None of the patients with ectopic ACTH secreting tumors had positive IPSS results. (sensitivity 65%, specificity 100%). In two patients where IPSS was done, no final diagnosis could be achieved due to lack of follow up.

In 14 out of 16 patients suspected to have CD with ≥50% suppression on HDDS and negative pituitary imaging, IPSS was carried out. Ratio was diagnostic in 9 patients in basal state. In 3 out of 4 patients who did not suppress on HDDS and had normal imaging findings, IPSS was done and ratio was diagnostic in all 3. In remaining one patient, results of all the 3 tests were negative. No major complications were encountered with the procedure. The diagnostic yield of various tests in localisation of CS is shown in Table 2.

Outcome

In all but one patient various combination of HDDS, imaging and IPSS established pre op diagnosis. Out of 69 patients with CD, 65 (30 micro, 14 macro, 7 doubtful, 13 normal, 1 empty sella syndrome) were subjected to TSS. Among the 4 patients not operated, 2 had microadenoma and 1 had negative imaging findings and 1 died before imaging could be done. Post op cure status was available in 52 patients wherein, 40 were cured (76%). Among the remaining 13 patients, 8 patients did not follow up and 5 patients died in the post op period. 23/30 (77%) of microadenoma, 5/14 (36%) of macroadenoma, 8/13 with normal pituitary imaging, and 4/7 with doubtful imaging finding were cured.

Three patients died of pyogenic meningitis and 2 patients died of pneumonia. Among the remaining patients, 4 patients developed CSF rhinorrhoea of which 1 developed pyogenic meningitis and recovered. All were treated conservatively. One patient developed deep vein thrombosis in post op period.

DISCUSSION

The reported sensitivity and specificity of HDDS in

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<th>Table 1 : Diagnostic distribution of cushing’s syndrome</th>
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<td>Number of patients</td>
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<td>Cushing’s disease</td>
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<td>Adrenal carcinoma</td>
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<td>Ectopic</td>
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<th>Table 2 : Sensitivity and specificity of various tests in localisation of cushing’s syndrome</th>
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the literature varies from 80 to 85% and 67 to 87% respectively when 50% suppression of serum cortisol was used as a cut off value. Our sensitivity (70%) and specificity (100%) of HDDS was comparable to literature. Accuracy rate of 86% using > 90% suppression of UFC and > 64% suppression of 17OHCs on HDDS is described. It needs to be pointed out here that results of HDDS, do not improve the pretest probability of CD, which is 85-90%.10

Sensitivity of imaging has been reported in various series ranging from 30% for CT scan and 50 to 60% for MRI.1-5 Our sensitivity (68%) of imaging was better than that reported in literature. Combination of HDDS and imaging localized the lesion in 90% of our patients. IPSS came through as an additional backup in problematic cases of suspected CD with negative pituitary imaging. In experienced hands the diagnostic sensitivity, specificity and accuracy of IPSS approaches 100%.12,13 It has emerged as an accurate and reliable means of distinguishing pituitary from non-pituitary ACTH dependent Cushing’s syndrome.

Sensitivity of IPSS in our center came up to 65% in spite of a cannulation rate of 100%. This was predominantly due to lack of availability of CRH. With combination HDDS, imaging and IPSS all patients but one could be correctly assigned the site of lesion. Complication rate of IPSS is related to experience and skill of radiologists. Though it is a safe procedure, morbid and even fatal complications are described with the procedure.

TSS in our center has a cure rate of 77% for microadenomas and 36% for macroadenomas, when basal post operative cortisol of < 5 mcg/dl is considered as criteria of cure. It needs to be noted that criteria of cure have varied in different series. When more stringent criteria of basal post operative cortisol of < 3.5 mcg/dl are applied, the cure rate will reduce to 48% in our series. TSS is a safe procedure in experienced hands with cure rates of 80 to 90% for microadenomas14,12 and less than 50%14,12 for macroadenomas as described in various series. CSF rhinorhoea was complication that was encountered in 4 of our patients, which settled on conservative management.

Five of our patients died in post operative period. Cushings disease is a serious disorder with increased risk of morbidity and mortality. Immune compromised state, muscle weakness due to cortisol excess and hypokalemia add to increased risk of infections, especially pneumonia and pyogenic meningitis.

All patients who were not cured/or had recurrence were evaluated de novo. Following reconfirmation of diagnosis as CD, 2nd TSS, RT, and bilateral adrenalectomy were the modalities of treatment in that order. 2nd TSS did not cure any of our patients (total 6 patients). RT cured 3 out of 10 patients. Two patients required additional bilateral adrenalectomy for cure.

Out of 52 patients where cure status was documented, 12 patients were not cured after TSS. In 7 out of 12 patients, no follow up was available. In the remaining 5 patients, 2 were subjected to second TSS (not cured) and three were subjected to RT. Total 2 patients out of 5 were cured with additional modalities of therapy. (1st patient: RT only, 2nd patient : TSS+RT+bilateral adrenalectomy).

Five patients, who had recurrence of disease, had a median duration of remission of two years. One out of five patients was lost to follow up after the diagnosis of recurrence. Four out of five patients were subjected to second TSS and none of them were cured. One patient died of lower respiratory tract infection in the post op period. Three out of five patients were given radiotherapy and two were cured. Remaining one patient required bilateral adrenalectomy for cure.

**CONCLUSION**

Key to the success in the management of patients with CS lies in accurate localization of site of lesion.2 In our center, combination of HDDS (overnight) in increasing concentration and imaging is used to arrive at diagnosis. In patients with ACTH dependent Cushing’s syndrome with negative imaging findings, IPSS helped to localize the site of lesion. Combinations of tests along with appropriate interpretation of data by an experienced endocrinologist are prerequisites for successful management of these patients. Combination of HDDS with imaging localized lesion in 90% of our patients whereas combination HDDS, imaging and IPSS could localize lesion in all but one patient.

IPSS is not routinely available in many centers. Even in the presence of negative imaging with HDDS pointing towards pituitary as a possible site, surgery may be justified. But if the results of both HDDS and imaging are inconclusive, IPSS would be necessary and patients should be managed at a center with experience in IPSS.

Patients with CS are metabolically unstable and they can deteriorate rapidly. Poor glycemic control, immune compromised state and hypokalemia that compounds their respiratory muscle weakness leading to delayed post op recovery are some of the problems encountered in management of these patients. Surgery as far as possible should not be delayed as sudden death due to LVF are reported in patients with CS.2 Respiratory muscle exercises along with control of all deranged metabolic parameters and hypertension are some of the pre operative measures which influence post op recovery of these patients.

Management of Cushing’s Disease is a team effort and is best carried out at a centre where both an experienced endocrinologist and neurosurgeon are available.

**REFERENCES**


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**Announcement**

"Academy of Cardiology at Mumbai - International and Indian Fellowship"

Academy of Cardiology at Mumbai invites applications for above fellowships (one each) for the year 2007 from eligible candidates. Applications alongwith detailed Curriculum Vitae and two letters of support from seniors in the profession should be sent to Academy of Cardiology at Mumbai, 102 Kirti Manor, S.V. Road, Santacruz West, Mumbai 400 054 by 1.2.2007.

Eligibility : D.M. or D.N.B. (Cardiology) from recognized centers and age 35 years or below. The fellowship will provide funding for training in interventional/non-invasive cardiology in prestigious centers upto 1 year. The interviews for selection will be conducted by Academy.