# Inferior petrosal sinus sampling (IPSS) to localize pituitary tumour in Cushing's disease: its feasibility in Sri Lanka

**S Pathmanathan[1], Noel P Somasundaram[2], C N Antonypillai[3], N Wijewardena[4], H Kularatne[5]**

*Sri Lanka Journal of Diabetes Endocrinology and Metabolism* 2011; **1**: 41-44

## Abstract

A 27-year-old woman who remained undiagnosed regarding the source of hypercortisolism for four years was referred for further investigations. Initial laboratory results confirmed endogenous hypercortisolism, (elevated 9 a.m cortisol and non suppressible low dose dexa-methasone suppression test) suggesting Cushing's syndrome. High dose dexamethasone suppression test did not suppress and serum adrenocorticotropic hormone (ACTH) level was elevated. MRI pituitary and CT abdomen, pelvis and chest also did not reveal any clue regarding the source of ACTH. Therefore venous sampling of Inferior-petrosal-sinus and mediastinal vessels was arranged. In the unstimulated inferior- petrosal- sinus- sampling (IPSS), there was a central-to-peripheral ACTH gradient, of 2.6 times (higher in centre) and right to left gradient of 2.1 times (higher on right) were noted suggesting the right pituitary as source of excess ACTH. Repeat MRI pituitary revealed a 0.5cm x 0.3cm poorly enhanced area in the right lobe of suggesting a microadenoma. She underwent Trans Sphenoidal Surgery (TSS) and the histology appearances were compatible with a pituitary adenoma. Thisi case illustrates the feasibility of venous sampling in localizing the source of ACTH secretion where imagings were inconclusive.

## Introduction

Endogenous overproduction of corticosteroids causes Cushing's syndrome. Common etiologies include pituitary-dependent adrenal hyperplasia (Cushing's disease), adrenal tumor, or a nonpituitary (ACTH)-producing tumor (ectopic Cushing's). Rarer causes include primary pigmented nodular adrenocortical disease, also called bilateral adrenal micronodular hyperplasia which includes the Carney complex and bilateral ACTH-independent macronodular hyperplasia. The most common of these etiologies is Cushing's disease (1,2), which causes significant morbidity and mortality that warrants early intervention. Inferior petrosal sinus sampling (IPSS) for ACTH is useful in some with Cushing's syndrome, that helps to distinguish Cushing's disease from other causes of Cushing's syndrome to guide optimal management. Furthermore, localization of an occult ACTH producing pituitary tumor in patients with Cushing's disease can help to lateralize the tumor and guide pituitary sparing surgery (3).

## Case report

A 27-year-old woman, who remained undiagnosed regarding the source of hypercortisolism for four years, was referred to our clinic for further investigations. She had initially presented with difficult to control hypertension and diabetes. On direct questioning she had facial puffiness, weight gain, easy bruising, oligomenorrhea and coarse facial features. In addition, she also experienced generalized weakness, depression, irritability, impaired memory and altered sleep. She had resistant hypertension which was controlled with captopril 50mg tid, hydrochlorothiazide 25 mg qd, atenolol 50 mg bid, prazocin 3g tid and frusemide 40 mg qd and diabetes was controlled with metformin 500 mg bid. Physical findings revealed a body mass index of 25.6 kg/m$^2$, a Cushingoid appearance with moon face, buffalo hump, hyperpigmentation, easy bruising, thin skin, proximal muscle weakness and purplish abdominal striae.

Initial laboratory results confirmed hypercortisolism, with an elevated 9 a.m cortisol of 35.7µg/dL (normal 5-25 µg/dL) and non suppressible low dose dexamethasone suppression test suggesting Cushing's syndrome. i.e following dexamethasone 0.5 mg 6 hourly for 48 hours 9 a.m cortisol was 28.3 µg/dL (normal <1 µg/dL). High dose dexamethasone suppression test did not show suppression i.e, (9 a.m cortisol was 35.7 µg/dL) following dexamethasone 2 mg 6 hourly for 48 hours 9 a.m cortisol

[1]*Senior Registrar, Endocrinology,* [2]*Consultant Endocrinologist,* [4]*Consultant Interventional Radiologist,* [5]*Consultant Neuro Surgeon, National Hospital of Sri Lanka,* [3]*Consultant Endocrinologist, Teaching Hospital, Kandy, Sri Lanka.*

was 27.9 µg/dL and elevated 9 a.m serum ACTH of 164 pg/ml (10-40 pg/ml). MRI pituitary and CT abdomen, pelvis and chest also did not reveal a possible source of ACTH. Noninvasive means of localizing the source of ACTH production also include the peripheral ovine corticotropin-releasing hormone (ovine CRH) stimulation test. Ovine CRH stimulation followed by peripheral venous sampling of ACTH is reserved for differentiating difficult cases of Cushing's disease and ectopic ACTH-secreting tumors. In pituitary Cushing's disease there is normal or exaggerated response to CRH whereas in ectopic ACTH-producing tumor there is no response to CRH. This test was not performed due to unavailability of ovine CRH. Venous sampling of Inferior-petrosal-sinus (IPS) and mediastinal vessels was arranged. Mediastinal sampling was done to identify extra pituitary source of ACTH. The commonest sources include bronchial carcinoids bronchial adenoma and thymus. So venous sampling of bronchial veins and thymic veins was arranged. Due to difficulty in cannulating the small veins sampling were done from right and left brachiocephalic veins and superior vena cava.

IPS sampling (IPSS) of ACTH after ovine CRH stimulation is an established invasive technique with a sensitivity and specificity of 100% for detection of a pituitary source of ACTH (3, 4). Because of the unavailability of ovine CRH unstimulated IPSS was performed. In the unstimulated IPSS, there was a central-to-peripheral ACTH gradient, of 2.6 times (higher in centre) as well as right to left gradient of 2.1 times (higher on right) was noted suggesting right pituitary as source of ACTH. A repeat MRI of the pituitary revealed a 0.5cm × 0.3cm poorly enhanced area in the right lobe of the pituitary gland suggestive of a microadenoma.

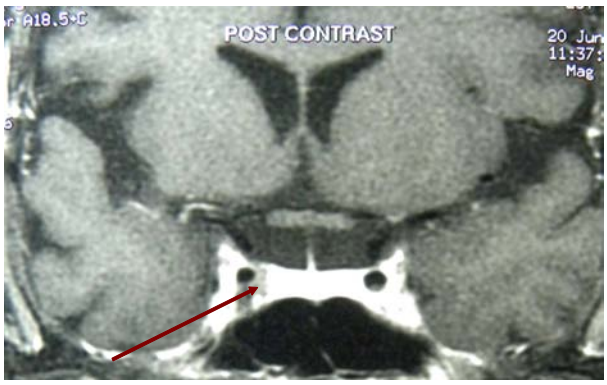



**Figure 1. MRI pituitary – arrow showing the micro adenoma.**

**Table 1. Unstimulated petrosal sinus and mediastinal vessels catheterization and sampling demonstrating the ACTH gradient between right and left petrosal sinuses and peripheral venous blood, suggesting right pituitary as the source**

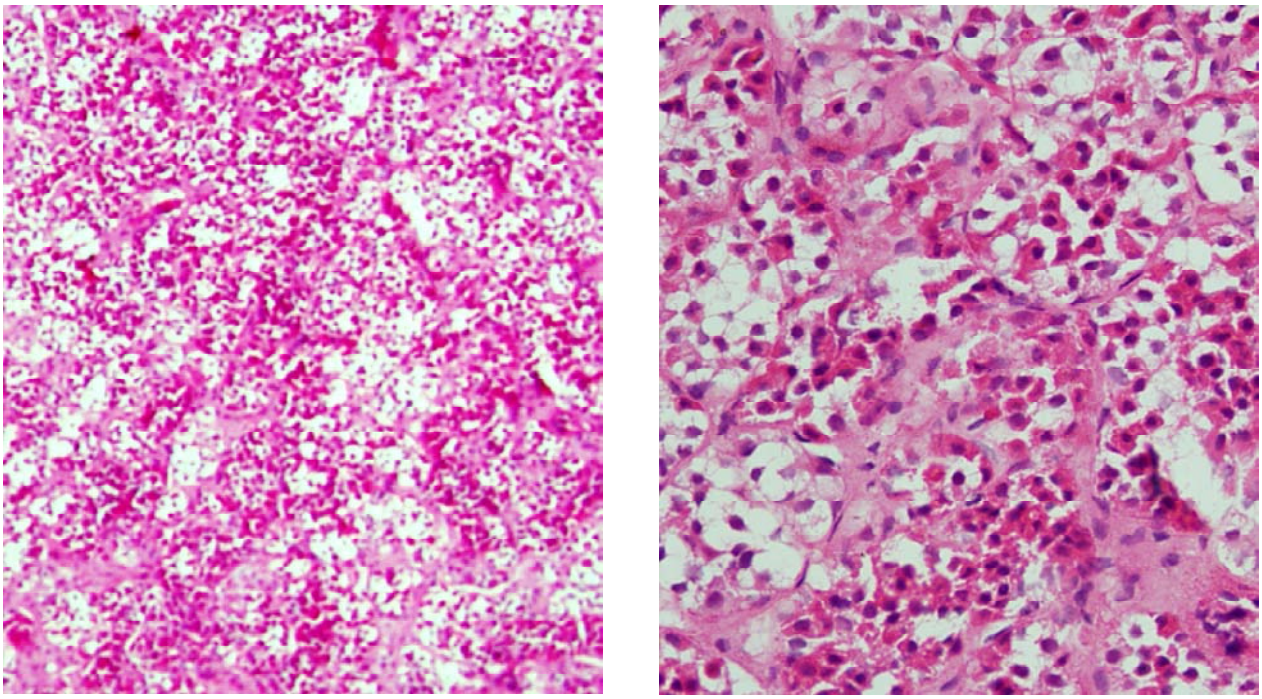
| | *Plasma ACTH levels* | |
|---|---|---|
| *Sampling sites* | *Right* | *Left* |
| Petrosal sinus | 434 pg/ml | 202 pg/ml |
| Inferior jugular vein | 380 pg/ml | 210 pg/ml |
| Brachio cephalic vein | 314 pg/ml | 210 pg/ml |
| Superior vena cava | 251 pg/ml | |
| Peripheral vein | 164 pg/ml | |

Abbreviations: ACTH, adrenocorticotropic hormone.

## Results

R/S petrosal sinus shows 2.6 times higher ACTH than in the peripheral veins.

R/S petrosal sinus shows 2.1 times higher ACTH than in the L/S.



A B

**Figure 2. A - In low power field and B - In high power field: Demonstrating the tumour cells with round nuclei with finely dispersed chromatin, distinct nucleoli and eosinophilic granular cytoplasm.**

Preoperatively her cortisol level was controlled with Ketaconazole 100 mg bid. She was on Ketaconazole for almost 3 years and the doses were adjusted according to her clinical symptoms and ketaconazole day curve. (The mean cortisol was maintained around 300nmol/L). She underwent trans sphenoidal surgery (TSS) and the histology was compatible with a pituitary adenoma. Immunohistochemistry for ACTH was not performed due to non availability in the government sector. 9 a.m cortisol post-operatively remained elevated at 964 nmol/L, suggesting a biochemical non-cure. (24 hours post operatively 3 doses of hydrocortisone which was given at 6 hourly interval were omitted and 9 a.m cortisol was performed.) She was restarted on Ketaconazole 100 mg bid and now awaits radiotherapy.

## Discussion

Ascertaining the cause of hypercortisolism in a patient with Cushing's syndrome can be a perplexing problem for the clinician. Two broad categories of hypercortisolism must be distinguished; those processes that are dependent on ACTH production and those that are not (2,4). Pituitary-dependent hypercortisolism accounts for over 70% of cases of Cushing's syndrome. The differentiation between pituitary and ectopic ACTH secretion is one of the most complex diagnoses in endocrine practice, and requires the integrated evaluation of biochemical tests and imaging techniques, none of which has a 100% diagnostic accuracy (2,4,5).

Measurement of plasma ACTH concentration before and after ovine corticotropin-releasing hormone (ovine CRH) stimulation reliably distinguishes ACTH-independent Cushing's syndrome (eg, functional adrenal tumors) from ACTH-dependent processes (6). The later comprise ACTH production from pituitary adenomas and from nonpituitary (ectopic) sources. The ideal therapy for ACTH-dependent Cushing's syndrome entails surgical removal of the ACTH-producing neoplasm. Thus, to guide appropriate intervention, one must accurately determine the source of ACTH production. Clinical history, dynamic biochemical tests (eg, dexamethasone suppression, ovine CRH stimulation), and CT or MR imaging (MRI) of the pituitary gland aid in distinguishing the two possibilities. Not infrequently, however, the clinical, biochemical, and imaging test results are indeterminate, resulting in uncertainty regarding the source of ACTH production. In such cases, inferior petrosal sinus sampling (IPSS) can help to resolve this uncertainty by accurately locating the source of ACTH production (3, 4, 6).

Inferior petrosal sinus (IPS) sampling (IPSS) was devised in an attempt to improve the diagnostic work-up of Cushing's syndrome. The rationale of this technique is that the pituitary gland drains directly into the IPSs, which is uncontaminated by blood from different sources. Therefore, in Cushing's disease, the concentration of ACTH is expected to be higher in the inferior petrosal sinus draining the hemi-hypophysis bearing the tumour

than the contralateral vessels. A ratio between inferior petrosal sinus (IPS) and peripheral basal (P) ACTH concentrations (IPS:P ratio) of 2:1 or greater is classically considered indicative of Cushing's disease. If corticotropin- releasing hormone (CRH) is used to stimulate ACTH secretion during IPSS, an IPS: P ratio of 3:1 or greater is classically considered indicative of Cushing's disease. In addition, a ratio between the right and left inferior petrosal sinus (IPS) of 1.4 or greater indicates that the adenoma is located on the corresponding side (3, 4, 5).

We report this case to highlight how IPSS helped to resolve the source of ACTH production. This patient first presented in 2007 and although the diagnosis of biochemical Cushing's syndrome was confirmed, and the cause of Cushing's syndrome was established as ACTH dependent, the source was not found. A plasma cortisol level higher than 50 nmol/L (2 μg/dL) postoperatively implies that the patient is not cured, indicating incomplete tumor removal (2,7). In optimal centers, cure rates are 80% to 90% for microadenomas and 50% for macroadenomas (2,8). Abnormal venous drainage can also lead to a false-positive gradient during IPSS. Even in cured Cushing's the risk of recurrence of Cushing's syndrome requires follow-up in all patients. Rate of recurrence increases with high postoperative cortisol values. Our patient also needs follow-up to decide on definite form of therapy whether resurgery or radiotherapy.

**References**


1. Plotz C, Knowlton A, Ragan C. The natural history of Cushing's syndrome. *Am J Med* 1952; **13**: 597-614.
2. Stewart PM. The adrenal cortex. In: Larsen P, Kronenberg H, Melmed S, et al., 11theds. Williams Textbook of Endocrinology. Philadelphia: WB Saunders; 2008 .
3. Johnson PL, Eckard DE. Inferior Petrosal Sinus Sampling www.mirs.org/Interventional %20 Radiology/rounds.htm
4. Connors JJ, Wojak JC. Inferior Petrosal Sinus Sampling. *Interventional Neuroradiology* 1999; 411-19.
5. Bonelli FS, Huston III J, Carpenter PC, Erickson D, Young WF Jr., Meyer FB. Adrenocorticotropic hormone-dependent Cushing's Syndrome: Sensitivity and Specificity of Inferior Petrosal Sinus Sampling. *Am J Neuroradiol* 2000; **21**: 690-6.
6. Colao A, Faggiano A, Pivonello R, Giraldi1 FP, Cavagninil F, Lombardi G. Inferior petrosal sinus sampling in the differential diagnosis of Cushing's syndrome: results of an Italian multicenter study. *European Journal of Endocrinology* 2001; **144**: 499-507.
7. Yawar A, Zuberi LM, Haque N. Cushing's disease and pregnancy: case report and literature review. *Endocr Pract* 2007; **13**(3): 296-9.
8. Nieman LK. Difficulty in the diagnosis of Cushing disease: *Nature Clinical Practice Endocrinology and Metabolism* 2006; **2**: 53-7.