

# Petrosal Sinus Sampling in the Diagnosis of Cushing's Syndrome: Preliminary Experience in University of Malaya Medical Centre

R Norlisah, FRCR\*, B J J Abdullah, FRCR\*, F L Hew, MRCP, S P Chan, FRCP

\*Department of Radiology and Department of Medicine, University of Malaya Medical Centre, 50603 Kuala Lumpur

## Summary

Differentiating between Cushing's disease of pituitary origin and ectopic ACTH syndrome of extra-pituitary origin remains a major challenge to the clinician because of limitations in the diagnostic accuracy of the high-dose dexamethasone suppression test. Routine use of inferior petrosal sinus sampling (IPSS) is therefore advocated by some authors for these patients. We present our preliminary experience of IPSS in 7 consecutive patients with Cushing's disease and discuss how the results impacted on the patients' management.

**Key Words:** ACTH-dependent Cushing's syndrome, Cushing's disease, Ectopic ACTH syndrome, Inferior petrosal sinus sampling (IPSS), High-dose dexamethasone suppression test (HDD).

## Introduction

Despite the advances in our understanding of pathophysiology, clinical diagnosis and management of Cushing's syndrome, the elucidation of its aetiology continues to be a challenge to most clinicians. Cushing's syndrome (CS) can be divided into 2 main categories namely, ACTH-dependent CS and ACTH-independent CS. The ACTH-dependent CS consists of pituitary (Cushing's disease) and ectopic secretion of ACTH by occult tumours outside the pituitary gland (EAS). The ACTH-independent CS consists of adrenocortical tumours (adenomas or carcinomas), bilateral micronodular and macronodular hyperplasia<sup>1</sup>. Cushing's disease

(CD) accounts for 80-90% while ectopic ACTH syndrome accounts for 10-20% of ACTH-dependent CS. The clinical, biochemical and radiological features of CD overlap with and are often indistinguishable from those of EAS syndrome<sup>2-4</sup>. Many of the tumours, both pituitary and ectopic, are small, making radiological localisation difficult.

Twenty four-hour urinary free cortisol (UFC) remains the accepted screening test, the measurement of ACTH helps to differentiate ACTH-dependent from ACTH-independent CS while the high-dose dexamethasone suppression test (HDD) is the primary investigation to

This article was accepted: 5 October 2002

Corresponding Author: Norlisah Mohd Ramli, Lecturer in Radiology, Department of Radiology, University of Malaya Medical Centre, 50603 Kuala Lumpur

distinguish between pituitary and ectopic ACTH secretion. HDD (2mg dexamethasone every 6 hours for 48 hours) is based on the observation that in CD, ACTH secretion still retains some degree of responsiveness to glucocorticoid negative feedback albeit at a higher threshold. A greater than 50% reduction of plasma cortisol level at the end of day 2 of the HDD test is considered a positive test for CD while an absence of such a degree of suppression suggests ectopic ACTH secretion. Using this cut-off point carries a sensitivity of 89-94% and a low specificity of 29-60%<sup>5,7</sup>. However, 20-30% of patients with ectopic ACTH secretion have been shown to suppress their plasma and urinary cortisol to less than 50% of baseline values during the HDD test<sup>8,9</sup> while as many as 20-30% of CD patients fail to suppress to less than 50%<sup>5,10</sup>.

Invitti and colleagues<sup>9</sup> reported fifty-five percent of patients with CD and 17% of those with EAS exhibited normal morning plasma ACTH levels, with values as low as 2 pool/L (9 pg/mL). ACTH levels were detectable (*i.e.* above the sensitivity of the assay) in 58% and within the normal range in 28% of patients with ACTH-independent CS. Therefore reliance on detectable ACTH levels alone to distinguish between the various aetiologies may result in misdiagnosis in some cases.

The corticotrophin releasing hormone (CRH) test using ovine or human CRH given intravenously and assaying plasma ACTH and cortisol response also carries variable specificity and sensitivity. CRH is not available in Malaysia, according to the list of registered products, Drug Control Authority, Ministry of Health Malaysia.

Pituitary imaging (CT / MR) is able to detect only about 50% of pituitary microadenomas of Cushing's disease<sup>11,12</sup>. Pituitary imaging has limited diagnostic value and is not used to decide on the need to proceed to surgery<sup>1,13</sup>.

Bilateral simultaneous sampling of the inferior petrosal sinus (IPS) is an accurate test with a high degree of sensitivity and specificity and provides the most direct method of diagnosing CD and distinguishing it from ectopic ACTH syndrome<sup>1,14</sup>. The high diagnostic accuracy<sup>15</sup> of this procedure has led some Centres and Endocrinologists to consider this a routine investigation in the work-up for ACTH-dependent CS. CRH stimulation during the IPSS has further improved the sensitivity of the procedure. A central: peripheral ACTH ratio of > 2 before and > 3 after the injection of CRH indicates CD. With time and wider experience with IPSS, reports of false-negative<sup>16,17</sup> and false-positive results<sup>18</sup> results are emerging. The lack of availability of expertise to perform IPSS and the potential complications occurring in this invasive test has limited its routine use in clinical practice<sup>19</sup>.

## Materials and Methods

IPSS was only performed after a definite diagnosis of CS was established by clinical findings, elevated 24-hour urinary cortisol level and overnight dexamethasone suppression test. All the patients had detectable levels of plasma ACTH that suggested ACTH-dependent CS even though some patients had functioning adrenal tumours (Table I).

The standard high dose dexamethasone (HDD) test was performed using 2mg of oral dexamethasone given every 6 hours for a total of eight doses. Baseline and 48 hour determinations of serum cortisol were made. The test was positive for CD when a fall in cortisol to less than 50% of baseline or to a level below 200 nmol/L at 48 hours.

When performing the IPSS, localisation of the femoral vein was achieved by anatomical landmarks and with the aid of colour Doppler ultrasound. We found that taping the patient's abdominal wall superiorly helped with visualisation of the groin in patients with central obesity.

Following a successful femoral vein puncture (13 out of 14 veins) a Cobra 5 F catheter with one end hole and side-hole was advanced over a hydrophilic wire (Road runner, Cook's USA) to manoeuvre catheter into petrosal sinuses. A petrosal sinus venogram was then performed with slow injection of contrast to confirm catheter placements. Reflux into cavernous sinus was avoided to prevent the theoretical risk of sinus thrombosis.

Four blood samples were taken at 5-minute intervals. Sampling of superior SVC, mid-thoracic SVC and mid IVC with simultaneous peripheral sampling for each of the sites was also performed to further enable localisation of tumour.

The central to peripheral ratio of ACTH was calculated. We used the maximum ratio obtained as recommended by the Oldfield study<sup>15</sup>.

## Results

Seven subjects underwent IPSS in UMMC (Refer to Table I). The ages ranged from 23-56 years with a median of 40 years. 6 out of 7 subjects were female. The most common clinical symptom was weight gain (7 out of 7), 5 out of 7 had striae; 4 out of 7 had hirsutism, proximal myopathy, easy bruising and elevated blood pressure; 3 out of the 6 women had amenorrhoea.

All the subjects had 24-hour urinary free cortisol levels of less than 700nmol/L, elevated plasma cortisol with a median of 1234nmol/L (range: 370-2098 nmol/L) and a loss of diurnal variation in cortisol levels. The diagnosis of CS was confirmed by the lack of suppression with the standard low dose dexamethasone test.

The HDD test was positive in 3 out of 7 cases. These results were consistent with operative and histological findings of pituitary adenomas. Of the 4 subjects who had negative HDD test, 2 were found to have adrenal adenomas, 1 had ectopic ACTH syndrome and 1 had a pituitary adenoma.

The 3 patients (MYL, HM, LSW) (Table I) with the positive HDD and IPSS were referred for pituitary surgery. Histology of the tumours removed confirmed pituitary adenomas and they all recovered fully and were eupituitary and has no Cushingoid features at follow-up 2-4 years after surgery.

The results revealed 1 false negative out of 4 cases of pituitary adenoma (CPK), if the HDD test results were relied on alone. This patient had an unusual small enhancing lesion in the posterior pituitary on MRI. He underwent transphenoidal pituitary surgery where the neurosurgeon identified and removed a microadenoma. Histologically this was confirmed to be a pituitary adenoma that stained positively for ACTH, prolactin and growth hormone. Clinically, this patient had a partial temporary improvement but had a relapse of his Cushing's after 3 months. He was scheduled for bilateral adrenalectomy but defaulted further follow-up.

All the subjects had gadolinium enhanced MRI pituitary. In all the cases of pituitary adenoma, the MRI correctly diagnosed the tumours. However in the case of bilateral pituitary adenoma (MYL), MRI only localise one of the tumours.

We were able to cannulate 11 out of 14 inferior petrosal sinuses. The mean central to peripheral ratio of ACTH was more than 2:1 in all the 4 patients with pituitary adenoma found at operation and confirmed on histopathological examination..

In one patient the IPSS correctly obtained elevated level of mean central to peripheral ratio ACTH in both petrosal sinuses. This patient was found to have bilateral pituitary adenomas on histology.

Mean central to peripheral ratio of ACTH in the superior vena cava is not elevated in any of the cases with pituitary microadenoma. The only case with elevated ratio was the patient with Ectopic ACTH syndrome, most likely an underlying Carcinoid as the 5-HIAA results were very high (LC) (Table I). Thoracic and abdominal CT scan of

Table 1: Summary of biochemical results, imaging, pathology findings and progress of patients

No Patient	Age	Sex	High dose dexamethasone		Baseline ACTH	IPSS central to peripheral ratio		CT thorax/Abdomen	MRI pituitary	Surgical Procedure	HPE results	Progress
			Baseline	48 H		Rt	Lt					
1	32	F	862	1091	29	1.15	1.43	Rt adrenal mass	Normal	Rt adrenalectomy	Adrenal cortical adenoma	Recovered
2	36	F	640	291	54	13.98	4.34	Nil	Rt microadenoma	Transphenoidal Rt microadenoma and biopsy of Lt.	Bilateral microadenoma	Recovered
3	56	F	370	572	107	Nil	Nil	Lt adrenal mass	Normal	Lt adrenalectomy	Lt adrenocortical adenoma	Recovered
4	29	F	786	349	10	0.73	5.46	Bilateral enlarged adrenals	Lt pit microadenoma	Transphenoidal removal of tumour	Lt pit adenoma ACTH	Recovered
5	51	F	1525	1363	735	0.92	1.1	Bilateral bulky adrenals	Empty sell	Nil	Ectopic ACTH?	Died of stroke
6	28	F	924	457	10	nil	2.81	Bilateral adrenal bulky/MRI	Lt microadenoma	Transphenoidal removal of tumour	Pit Lt microadenoma	Recovered
7	23	M	998	611	56	1.2	5.2	Nil	Enhancing area post pituitary	Transphenoidal removal of tumour	Pit adenoma	Recovered but relapsed 3 months

that patient did not reveal any mass. Unfortunately, she suffered a stroke that left her with major neurological deficits. The family declined further investigations and treatment.

Inferior petrosal sinus catheterisation was successful in 11 of 14 attempts. The technical failure was due to difficulty in cannulation of the femoral vein (1 patient) and both inferior petrosal sinuses due to Shiu Type IV variations.

In one patient, there was a possible puncture of the right atrial wall. The patient had chest pain for 48 hours after the procedure, which subsided with analgesics. There were no ECG changes and an urgent 2-D echocardiography did not reveal any pericardial collection. The patient recovered well.

## Discussion

The Inferior Petrosal Sinus drains the cavernous sinuses to the internal jugular veins. It extends postero-inferiorly from the cavernous-sinus and runs back in groove between the petrous temporal and basilar occipital bones. It is a cone shaped vessel that measures approximately 23-28mm. It usually leaves the cranial cavity through the jugular foramen and is separated from the rest of the foramen by an anterior petro-occipital ligament. It sometimes drains by a vein in the hypoglossal canal to the suboccipital vertebral plexus.

As it enters the jugular foramen, the IPS becomes a vein, approximately 2-mm in diameter, and then joins the jugular vein directly. The junction of IPS into the jugular vein is usually 6mm inferior to the level of its entrance into the jugular foramen, most commonly at the inferior margin of the foramen. There are variations in which the junction may be either within the foramen, extracranially, intracranially or within the sigmoid sinus.

The Shiu system classifies the IPS and basilar plexus (BP) drainage system into 4-types. Type 1 (10-45%) describes the IPS descend directly into

the superior bulb of the internal jugular vein. Type II (24-47%) describes the IPS that drains into the common trunk shared by IPS and the deep cervical venous plexus. This common trunk then drains directly into the superior jugular bulb. Type III (24-37%) describes an IPS that is replaced by a plexus of veins. Type IV (1-7%) describes a well-formed IPS that drains directly into the deep venous plexus.

In our study, the 6 patients had a Type I variation as described by Shiu et al. One patient where we failed to cannulate the petrosal sinus demonstrate a Type IV variation with no communication with the internal jugular vein bilaterally.

The 7 patients who underwent the IPSS procedure were pre-selected. Four already had visible pituitary lesions on MRI and IPSS was done to record the hormonal activity of these lesions. The other three had IPSS to resolve inconsistencies in their dynamic hormonal profiles, i.e. presence of detectable ACTH levels while having unilateral or bilateral adrenal lesions on CT scan of the abdomen. The IPSS results either reinforced the diagnosis or directed the physician to the correct diagnosis and appropriate management.

CT has been reported to be 47% and MRI 77% sensitive, for detection of pituitary adenoma<sup>21</sup>. The IPSS is reported to be accurate in 99% of patient with CD and 100% sensitive and specific with CRH stimulation<sup>14</sup>. However Wiggam and colleagues<sup>20</sup> recently reported 82% sensitivity in their experience with 45 patients who had IPSS without CRH. We demonstrated almost similar findings without CRH stimulation. Several clinical studies have demonstrated that interpetrosal gradient; can accurately lateralise microadenomas within the pituitary gland<sup>1,22</sup>.

In several studies<sup>23,24</sup> IPSS with ovine CRH has been proven to be a more sensitive and specific for the diagnosis of CD. However due to lack of availability of CRH, the stimulation test was not attempted in this study.

The technical challenges that we faced during the procedure were similar to those described by Miller and Doppman<sup>24</sup>. This includes the common femoral vein puncture, the crossing of the left internal jugular vein and the catheterisation of the Inferior Petrosal Sinus. We also faced added difficulty in manoeuvring the catheter in the cardiac region.

## Conclusion

Bilateral simultaneous sampling of the IPS is a valuable test for differentiating Cushing's disease from the ectopic ACTH syndrome. It has an

integral role in assisting the clinician in managing the patient with ACTH-dependent Cushing's syndrome. In our experience, it is a technically challenging procedure that can be successfully performed without any major complications.

## Acknowledgements

This study was funded by the International Medical University (Research No. IMU003/2000). The authors wish to thank the Director of Health, Negeri Sembilan, for permission to conduct this study.

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