BILATERAL INFERIOR PETROSAL SINUS SAMPLING (IPSS) – DDAVP/desmopressin protocol

1. Introduction

1.1 Scope and purpose

The purpose of this procedure is to describe the protocol for performing the Inferior petrosal sinus sampling (IPSS) procedure using desmopressin (DDAVP). This DDAVP protocol is used in place of the protocol utilising CRH as a stimulant.

1.2 Responsibility

The protocol will be jointly implemented between clinical biochemistry staff, endocrine clinical team, and interventional radiology

1.3 Definitions

- IPSS – Inferior petrosal sinus sampling
- DDAVP – desmopressin
- CRH – Corticotrophic releasing hormone
- ACTH – adrenocorticotrophic hormone

1.4 Indications

Patients with Cushings syndrome and high ACTH levels without a definite pituitary source. The aim of the test is to differentiate between pituitary from a non-pituitary sources of ACTH release

1.5 Contra-indications

- Allergy to contrast dye
- Ischaemic heart disease
- Orthopnoea
- Bleeding tendency

1.6 Side effects

- The use of DDAVP can come with side effects of headache and vomiting
- The procedure carries a risk of transient flushing, ear/head discomfort/headache, <1% risk of stroke, small PE risk

2. Preparation

2.1 Ensure 10ug Desmopressin for intravenous injection is ordered from pharmacy ahead and collected before the day of procedure. It should be prescribed on a medication prescription chart for administration on the day of procedure

2.2 A day procedure bed should be requested under interventional radiology with an overnight bed with neurosurgery if complications from procedure arise

2.3 Ongoing excess cortisol production should be confirmed within 1 week of the planned procedure through a repeat 24hr urine free cortisol or dex suppression test or salivary cortisol collection.

2.4 The endocrinologist will need to tell the patient to stop metyrapone or other agents to control Cushing's one week before the procedure. They must not eat any food for 4 hours prior to the procedure but can take clear fluids and their usual medication beforehand. They should be informed not to drive on the day of the procedure and will need someone to collect them

2.5 Consenting for the procedure should include possible complications from the DDAVP and from the catheter positioning

2.6 Clinical Biochemistry should be contacted at least 2 weeks before the planned procedure through the duty biochemist or other known contacts (Dr Michelle Young michelle.young@nbt.nhs.uk or Dr Nathan Cantley Nathan.cantley@nbt.nhs.uk) to ensure that a clinical scientist/chemical pathologist is present to take collected samples.

2.6.1 They should attend with prelabelled sample tubes and an ice box with plenty of ice. 15x EDTA and 15x Li-Hep tubes should be brought labelled as per the table below.

2.6.2 Samples should be requested on the day of procedure on laboratory management system (Winpath) as individual sample numbers

2.6.3 The patient will have pre-operative assessment arranged via the skull base nurses in neurosurgery.

3. Procedure

3.1 Members of the team who should be present in the room

3.1.1 Member of the endocrinology team for the prescription of DDAVP and assist with sample collection

3.1.2 Member of the biochemistry team for the collection of samples at appropriate times

3.1.3 Interventional radiology team members for catheter placement

3.2 Catheters should be placed as per IR procedure in both inferior petrosal sinus's and a further catheter placed in a peripheral vein (e.g. peripheral femoral catheter at point of arterial puncture)

3.3 At the point of catheters all being placed and confirmed in correct position, Desmopressin should be drawn up into an appropriate syringe ready to administration

3.4 Prior to commencing sample collection all those involved in the sample collection in the procedure should agree on order of draw from catheters

3.5 This should include a system of clearly identifying laterality of samples to the clinical biochemist aliquoting samples into tubes

3.6 It should also be communicated to ensure a draw and discard of 5mls is done prior to the draw from the catheters for the blood sample to be used. This is due to saline administration keeping flow through the catheter patent giving rise to a potential sample dilution/drip arm effect in the sample

3.7 Sample draw order

3.7.1 Samples to be taken are outlined in the sample table shown in *Appendix A.* An 8-10ml draw should be taken from each catheter to give 4ml sample for each tube, for each catheter, for each time point

Please note: Samples for ACTH kept on ice are stable for 1 hr unseparated but need to be spun and separated within this timeframe to avoid analytical problems. If there is a delay between first sample draw and completing the procedure, samples taken up to that point should be brought back to the lab and processed.

3.7.2 Basal samples – Take samples for -15mins and 0mins as described above

3.7.3 Administer Desmopressin – Once 0min samples taken, give 10ug Desmopressin IV through peripheral catheter as bolus with saline flush

3.7.4 Take stimulation samples – Take +5, +10, +15 samples as described above

3.7.5 Remove catheters – Once all samples confirmed taken and aliquoted into all sample tubes, remove catheters as per IR protocols with appropriate haemostasis/dressing

3.7.6 Post procedure care – Patients should be observed for complications as per standard interventional radiology practice. If required, patient should be observed overnight but responsibility for this lies with IR/neurosurgical teams

4. Sample processing and reporting

4.1 The clinical biochemist will return to the lab with samples and ensure sample handling processes are followed with appropriate and accurate labelling of samples separated and aliquoted. Labelling should be second checked by another member of appropriately trained lab staff

4.2 Samples for ACTH should follow sendaway procedures and be followed up for results in 3 working days

4.3 Once all results are returned and confirmed, they should be inputted into the reporting template spreadsheet as attached and second checked by another member of staff to check for transcription error.

4.4 A standard report should be collated as per the reporting template in '*Appendix B'* and sent to the endocrinology and IR teams who requested the procedure. The report once finalised should be added to the patients electronic record

5. Interpretation

5.1 A central to peripheral ACTH ratio of >2 prior to CRH or >3 post CRH is very suggestive of pituitary dependent disease.

5.2 False positive results are rare, false negative results are reported as low (~4%) and occur secondary to anatomical variations, technical sampling issues or unusual ACTH tumour secretion[3].

5.3 Prolactin measurement during IPSS may improve diagnostic accuracy and decrease false-negative results[4]. Baseline central to peripheral prolactin ratio ≥1.8 suggests successful catheterization during IPSS (prolactin-normalised central to peripheral ACTH ratios may be used to differentiate between a pituitary and ectopic source of ACTH. Values of 0.7 or lower are suggestive of ectopic ACTH syndrome and those 1.3 or higher are indicative of Cushing disease).

5.4 An interpretation guide/algorithm is in appendix 3 for reference

6. Sensitivity and specificity

6.1 An overall sensitivity of 96% and specificity of 100% in differentiating Cushing disease from ectopic ACTH secretion is reported using this method[1,2].

7. References

- Castinetti F, Morange I, Dufour H, Jaquet P, Conte-Devolx B, Girard N, Brue T. Desmopressin test during petrosal sinus sampling: a valuable tool to discriminate pituitary or ectopic ACTH-dependent Cushing's syndrome. Eur J Endocrinol. 2007 Sep;157(3):271-7. doi: 10.1530/EJE-07-0215. PMID: 17766708.
- Deipolyi AR, Alexander B, Rho J, Hirsch JA, Oklu R. Bilateral inferior petrosal sinus sampling using desmopressin or corticotropic-releasing hormone: a single-center experience. J Neurointerv Surg. 2015 Sep;7(9):690-3. doi: 10.1136/neurintsurg-2014-011262. Epub 2014 Jul 4. PMID: 24996436
- Newell-Price J, Trainer P, Besser M, Grossman A. The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. Endocr Rev. 1998 Oct. 19(5):647-72
- Oldfield EH, Doppman JL, Nieman LK, Chrousos GP, Miller DL, Katz DA. Petrosal sinus sampling with and without corticotropin-releasing hormone for the differential diagnosis of Cushing's syndrome. N Engl J Med. 1991 Sep 26. 325(13):897-905.
- Bonelli FS, Huston J 3rd, Carpenter PC, Erickson D, Young WF Jr, Meyer FB. Adrenocorticotropic hormone-dependent Cushing's syndrome: sensitivity and specificity of inferior petrosal sinus sampling. AJNR Am J Neuroradiol. 2000 Apr. 21(4):690-6.
- Sharma ST, Nieman LK. Is Prolactin Measurement of Value during Inferior Petrosal Sinus Sampling in Patients with ACTH-dependent Cushing's Syndrome?. J Endocrinol Invest. 2013 Jul 26.

Appendix 1 – sample table

Bilateral inferior petrosal sinus sampling worksheet table

Patient name
NHS number
Date of procedure
Biochemist present
Endocrinologist present
IR Consultant present

Time (mins)	Left petrosal sinus			Right petrosal sinus			Peripheral		
	ACTH	Cortisol	PRL	ACTH	Cortisol	PRL	ACTH	PRL	Cortisol
-15	[1]	[2]		[3]	[4]		[5]	[6]	
0	[7]		[8]	[9]		[10]	[11]	[12]	
+5	[13]		[14]	[15]		[16]	[17]	[18]	
+10	[19]		[20]	[21]		[22]	[23]	[24]	
+15	[25]		[26]	[27]		[28]	[29]	[30]	

Appendix 2 – reporting template

Department of Clinical Biochemistry
Core Clinical Services Directorate
Pathology Sciences Laboratory
(Blood Sciences and Bristol Genetics)
Southmead Hospital
Westbury on Trym
Bristol
BS10 5NB
Tel:
Email:
Date:

BILATERAL INFERIOR PETROSAL SINUS SAMPLING (IPSS) REPORT

Name:	**NHS Number**:
MRN:	**Address**:
Date of Birth:	**Consultant Endocrinologist**:
Procedure Date:	**Consultant Radiologist**:
Stimulation used: [Desmopressin or CRH]	

The following is an interpretative report from the IPSS performed on the above patient.

Absolute Results from the procedure

Time (mins)	Left petrosal sinus			Right petrosal sinus			Peripheral		
	ACTH	Cortisol	PRL	ACTH	Cortisol	PRL	ACTH	Prolactin	Cortisol
-15									
0									
+5									
+10									
+15									

Units used: Cortisol nmol/L, ACTH ng/L, prolactin mIU/L

Calculated IPS to peripheral ratios for prolactin and ACTH

Time (mins)	Left petrosal sinus			Right petrosal sinus			Peripheral		
	ACTH	Cortisol	PRL	ACTH	Cortisol	PRL	ACTH	Cortisol	Prolactin
-15									
0									
+5									
+10									
+15									

Interpretation

A central to peripheral ACTH ratio of >2 prior to CRH or >3 post CRH is very suggestive of pituitary dependent disease.

In patient [insert], there is [insert interpretation].

False positive results are rare, false negative results are reported as low (~4%) and occur secondary to anatomical variations, technical sampling issues or unusual ACTH tumour secretion. Prolactin measurement during IPSS may improve diagnostic accuracy and decrease false-negative results.

During IPSS prolactin-normalised central to peripheral ACTH ratios may be used to further differentiate/confirm a pituitary and ectopic source of ACTH.

Values of 0.7 or lower are suggestive of ectopic ACTH syndrome and those 1.3 or higher are indicative of Cushing disease. Prolactin-normalised central to peripheral ACTH ratio =

$$\frac{\text{Dominant peak post-CRH IPS:ACTH/Peripheral post-CRH ACTH}}{\text{Ipsilateral basal IPS Prolactin/Peripheral basal Prolactin}}.$$

[In this patient the prolactin normalised central to peripheral ACTH ratio for the dominant ACTH level was on the [insert] side / [peripheral]. This further confirms [ectopic / pituitary dependent disease as the overall interpretation].

Central to peripheral prolactin ratios >1.8 indicate successful catheterisation which is present in the samples used for the above interpretation. [insert interpretation]

Please get in contact to discuss if any further interpretation is required or any questions relating to the interpretation of raw results and ratios.

[signature]

[name]
[role]

Appendix 3 - interpretation

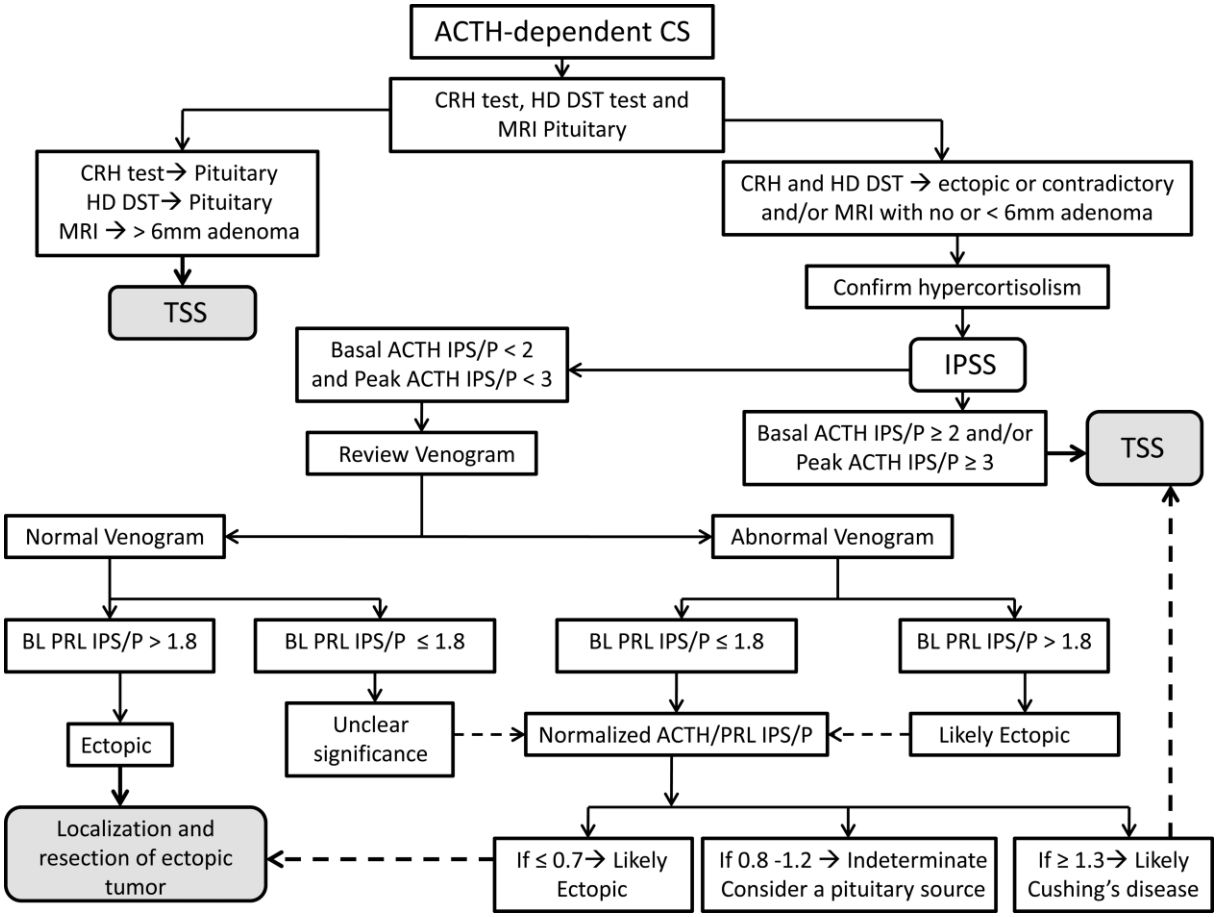

Figure 1.

Suggested algorithm for evaluation of ACTH-dependent Cushing's syndrome. BL, Baseline;CS, Cushing's syndrome; HD DST, high-dose dexamethasone suppression test; PRL,prolactin; IPSS, inferior petrosal sinus sampling; IPS/P, inferior petrosal sinus to peripheral; TSS, transsphenoidal surgery. *Adapted from "Prolactin as a marker of successful catheterization during IPSS in patients with ACTH-dependent Cushing's syndrome" by Sharma ST, Raff H and Nieman LK, 2011, J Clin Endocrinol Metab; 96(12):3687-94*

Appendix 4 – Patient information leaflet

Inferior petrosal blood sampling procedure

Introduction

- You have been diagnosed with Cushing's syndrome, a condition where there is excessive production of a hormone called cortisol by your adrenal glands.
- In your case, your adrenal glands are being stimulated by excessive production of adrenocorticotropic hormone (ACTH) usually produced by a pituitary lesion.
- Less commonly excessive production of ACTH may occur from other parts of the body.
- The purpose of this test is to see whether the excess ACTH is coming from your pituitary gland.
- This is a procedure in which multiple blood samples are obtained from the main veins draining the pituitary gland, following the injection of a substance that activates secretions of pituitary hormones. You have been referred for this procedure since this is the only reliable way to obtain these blood samples.

- If the test confirms that your pituitary is producing excess ACTH then pituitary surgery may be recommended, otherwise further investigations may need to be carried out to look for the source of ACTH production.
- The procedure is performed on an outpatient basis and takes place in the X-ray department at Southmead Hospital.
- It is important that you have someone at home to look after you on the evening and night after the procedure.

- If you have an allergy to contrast, heart problems, bleeding problems or are unable to lie flat for a period of time then please let us know as you may not be able to have this procedure. It is also important that you inform the department in advance if you are diabetic or if you are on warfarin or any other medicine to thin the blood.

Procedure

- If you are taking medications called Metyrapone or Ketoconazole, you must discontinue them one week before the procedure.
- You are requested to fast for 4 hours before the procedure but should drink water normally to avoid dehydration. Please also have a bath and shave over the groins on both sides.
- On the day of the test, you will meet the radiologist who will explain and who will carry out the procedure. If you are happy to proceed, you will be asked to sign a consent form.
- During the procedure you will be asked to lie flat on a special X-ray table. The skin in both of your groins will be cleaned with cold fluid before you are given an injection of local anaesthetic to numb the area. You should not feel any pain following this, but you will feel some gentle pushing as catheters (special plastic tubes) are inserted into the main vein in each groin. The catheters are then guided through the veins up into the vein near your pituitary gland.
- The catheters are guided through the veins up to the vein near your pituitary gland with X-ray guidance to ensure their positions are correct.

- A series of blood samples will then be taken. During this time you will also be given an injection of a hormone, called Desmopressin, through one of the catheters. This may cause you to feel a 'flushing' sensation for a few seconds.

- After the blood samples have been collected, the catheters will be removed and gentle pressure applied to your groin area for a few minutes to help stop bleeding.
- You will be asked to lie flat for a little longer and then gradually sit up and mobilise. If there are no complications then you will be allowed home on the same day. You will need somebody to collect you as you should not drive for 1 day.

Risks

- Bruising and bleeding may occur at the groin puncture sites
- Serious complications are very rare but may include stroke and blockage of vessels
- There is a very low risk of having leg clots

Results

- The results of this test will be reviewed by your endocrinologist and will be discussed with you at your next appointment.

Appendix 5 – Visual interpretation guide