

Petrosal Sinus Sampling in Cushing's Disease

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Cushing's Syndrome

- Exogenous etiology = Iatrogenic
- Endogenous etiology
 - Pituitary adenoma (CD)- 60-80% of cases
 - ACTH secreted and slightly elevated or normal (normal level in face of elevated cortisol is inappropriate)
 - Ectopic ACTH production- 1-10% of cases
 - Oat cell carcinoma of lung, thymomas, islet cell tumors of the pancreas, carcinoid tumors, medullary carcinoma of the thyroid, pheochromocytomas
 - ACTH very elevated
 - Hypothalamic or ectopic release of CRH (pseudo-Cushing's state)

Clinical Findings

- Hypertension
- Ecchymoses and purple striae on flanks, breasts, and lower abdomen
- Hyperglycemia
- Amenorrhea, impotence, reduced libido
- Hypokalemia
- Hyperpigmentation of skin and mucous membranes
- Weight gain
- Atrophic tissue with easy bruising
- Depression, emotional lability
- Osteoporosis
- Generalized muscle wasting
- Easy fatigability
- Elevation of other adrenal hormones: androgens may cause hirsutism and acne

Inferior Petrosal Sinus Anatomy

- Type 1
 - IPS with large anastomosis to IJV and small anastomoses with VVP
- Type 2
 - IPS with large anastomosis to IJV and large anastomosis with VVP
- Type 3
 - Numerous IPS channels into IJV
- Type 4
 - No anastomosis with IJV and large anastomosis with VVP

Complications of IPSS

- Brainstem hemorrhage
- Brainstem stroke
- Venous subarachnoid hemorrhage
- Pulmonary embolism

Techniques for ACTH Sampling

- IPSS
 - Unilateral double 6F sheaths into CFA or bilateral 6F sheaths
 - 5F catheter placed into each IPS or .018 inch microcatheter placed into each IPS
 - IPS plasma samples evaluated at various time periods for ACTH
 - Peripheral blood sampled at various time periods for ACTH and cortisol
 - 1.0 microgram/kg CRF given at 0 minutes (increases diagnostic accuracy from 61% to 92% in some papers)
 - Plasma sampled at 10 minutes from other sites to rule out an ectopic source

Sampling Error

- A hypoplastic (Type 4) IPS or plexiform IPS (Type 3) can create sampling errors and lead to a false negative study
- 0.8% according to Doppman
- False positive studies have also been seen when IPSS is carried out during periodic hormonogenesis. Therefore, a patient must be hypercortisolemic at the time IPSS is performed for the study to be valid.

IPSS Success

- 55-99% success rate at performing the procedure and obtaining useful data
- If IPSS is negative and MR is negative and an ectopic source is not located, continue to follow with MR since IPSS might be falsely negative



Plasma Ratios

- Bilateral IPS/P ratio > 2 at 5 minutes after CRF administration has had a sensitivity of 97% and a specificity of 100% in diagnosing CD
- Ratios of gradients between each IPS > 1.4 at 5 minutes after CRF stimulation correctly lateralizes a lesion in 83% of cases compared to 72% correct lateralization with MRI

IPSS Alternatives

- Superselective cavernous sinus sampling without CRF stimulation
- As sensitive as IPSS with CRF stimulation
- 100% correct lateralization of the adenoma compared to 87% with IPSS
- Some false lateralizations with midline tumors

Sampling Alternatives

- Single blood samples without sequential sampling
- CRF stimulation used
- Single IPS/peripheral ratio > 2 as accurate as multiple sample method
- Avoids need for prolonged period of indwelling catheter

MRI vs IPSS

- J Clin Endocr and Metab 83:2291-5, 1998
 - Accurate localization of pituitary lesion was more frequent with IPSS than MR (70% vs. 49%)
- Clinical Endocrinology 45(2)147-156, 1996.
 - MRI correctly demonstrated adenoma in 68.8% of cases and correctly lateralized it in 63.6% of cases
 - IPSS correctly indicated adenoma in 90% of cases without CRF and in 95.8% of cases with CRF and correctly lateralized it in 66.7% of cases.

Pseudo-Cushing's Disease

- IPS CRF levels are not easily measured and cannot be used to determine whether individual patients may have hypersecretion of CRF causing their ACTH secretion

CT and MRI vs IPSS

- Clinical Endocrinology 40(4):485-492, 1994.
 - CT correctly lateralized 30% of adenomas
 - MRI correctly lateralized 37% of adenomas
 - IPSS with CRF stimulation correctly lateralized 80% of adenomas

MRI vs IPSS

- Clinical Endocrinology 40(1):87-92, 1994.
 - IPSS identified CD in 88% following CRF
 - IPSS lateralized the lesion in only 55% of cases when technical failure was taken into account
 - MRI and IPSS concordance for lateralization was seen in 64% of cases after CRF
 - IPSS and surgery were concordant for lateralization in 73% of cases after CRF
 - Recommend IPSS only if MRI is equivocal

Sampling Alternatives

- Bilateral sampling of IJV post CRF stimulation
 - Central/peripheral ratios >2 pre CRF and >3 post CRH had sensitivity of 80%
 - IPSS sampling had 90% sensitivity
- Consider doing IPSS only when IJV sampling technique is negative

Sampling Alternatives

- CRF not available in Australia in 1997
 - Used metyrapone instead (reduces cortisol production by inhibition of 11 β -hydroxylation reaction) 750 mg PO q6 hrs x 4 prior to IPSS
 - In Cushing's patients the ACTH response to a reduction in cortisol is greater than expected a normal individual or in one with ectopic ACTH production
 - Ratio 12.9 for M+ patients, 9.8 for M- patients and 1.6 for M+ ectopic patients
 - Testing was correct in all patients and correctly lateralized 85%

Vasopressin and IPSS

- Higher AVP levels have been found in the IPS ipsilateral to the ACTH secreting adenoma than in the contralateral one
- AVP higher in the IPS in CD than in other pituitary disorders
- Patients with CD and poor surgical outcomes had the highest IPS AVP levels
- Is it possible that AVP is responsible for the persistence of ACTH hypersecretion in some patients that respond poorly to surgery

Adenoma Lateralization

- IPSS may not correctly lateralize the adenoma
- Some studies show correct lateralization in only 70% of cases due to shunting of blood toward the side of dominant drainage
- Therefore, all patients undergoing IPSS must have venography to determine the type of drainage they present so as to determine its effect on ACTH values.
- Some even feel that a dominant IPS is found on the side of the dominant half of the adenohypophysis

