Bilateral inferior petrosal sinus sampling



Inferior petrosal sinus sampling (IPSS) is an invasive procedure in which adrenocorticotropic hormone (ACTH) levels are sampled from the veins that drain the pituitary gland; these levels are then compared with the ACTH levels in the peripheral blood to determine whether a pituitary tumor (as opposed to an ectopic source of ACTH) is responsible for ACTH-dependent Cushing syndrome. IPSS can also be used to establish on which side of the pituitary gland the tumor is located.

Bilateral inferior petrosal sinus sampling (BIPSS) is considered the gold standard test for anatomical localization for Cushing's disease where radiology has been inconclusive ¹⁾.

In a metaanalysis of 21 studies, the overall sensitivity and specificity of BIPSS were found to be 96% and 100% respectively $^{2)}$.

Anatomical localization of pituitary neuroendocrine tumor can be challenging in adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome, and bilateral inferior petrosal sinus sampling (BIPSS) is considered gold standard in this regard. Stimulation using corticotropin releasing hormone (CRH) improves the sensitivity of BIPSS.

In essence, it tests to see the source of the raised ACTH levels in a patient with diagnosed Cushing's syndrome and high or normal serum ACTH levels. The inferior petrosal sinus is where the pituitary gland drains. Therefore, a sample from here showing raised ACTH compared to the periphery suggests that it is a pituitary cause of Cushing's, i.e. Cushing's disease. Equivocal levels of ACTH indicate ectopic or Paraneoplastic Cushing's Syndrome. The sample is usually taken after administration of Corticotropin-releasing hormone or, more recently, DDAVP, which have been shown to increase ACTH production in active ACTH-producing pituitary tumors. Increasingly, it is known as a gold-standard method for diagnosing Cushing's disease.

To increase the sensitivity, the sampling is repeated after peripheral administration of oCRH. Following this a peak central to peripheral plasma ACTH ratio of 3 or more occurring 3-5 minutes after oCRH stimulation is highly indicative of Cushing disease.

see Inferior petrosal sinus sampling with desmopressin.

Asymmetric inferior petrosal sinuses (IPS) are not infrequently encountered during bilateral IPS

sampling. There is little data on whether IPS symmetry influences success in predicting the adenoma side in patients with ACTH-dependent Cushing's syndrome (CS).

BIPSS was performed in 38 patients with a mean age of 45 ± 15 years. The overall technical success rate was 97% for bilateral cannulation. Asymmetric IPS were observed in 11 (39%) patients with Cushing's disease (CD). A side-to-side ACTH ratio was not significantly different between patients with symmetric outflow and those with asymmetric outflow at baseline (8.6 ± 2.7 versus 16.4 ± 6.0 ; P = 0.45), but ratios were significantly different after ovine corticotropin-releasing hormone (oCRH) stimulation (6.0 ± 2.5 versus 35.7 ± 22.5 ; P = 0.03). BIPSS correctly predicted the side of the adenoma in 25 (96%) patients with CD. Prediction was better when the venous outflow was symmetric (100%) rather than asymmetric (93%), although the difference was not significant (P = 0.42). Remission from CS was achieved in 32 patients (87%), independent of the symmetry of IPS.

Bearing in mind the sample size of this audit, asymmetric IPS at least do not seem to diminish the accuracy of diagnosis of ACTH-dependent CS, nor do they influence the clinical outcome ³⁾.

Procedure

Most often, BIPSS is performed by sampling ACTH peripherally and from both IPSs before and after CRH (Acthrel; Ben Venue Laboratories, Ohio, USA) administration. In the US, CRH is typically given at a dose of 1 µg/kg, by slow intravenous push over 30 seconds; in other countries, a typical dose is 100 µg. Conscious sedation is preferred to allow for the monitoring of symptoms suggesting complications. A 6-French sheath is advanced into the right femoral vein, and a five-French sheath into the left femoral vein. The larger sheath allows for sampling from the common femoral vein, while a 5-French catheter is in place distally. Subsequently, 3,000–5,000 units of heparin are given to prevent cavernous sinus and other venous thrombosis.

Next, 5-French Davis catheters are advanced through each femoral vein sheath into the contralateral internal jugular vein, followed by 2.8-French microcatheters, directed medially at the C1–2 level to access the orifice of the IPS⁴. without entering clival veins⁵. Both catheters are positioned symmetrically.

Once catheter positions are confirmed, two baseline ACTH specimens are collected from the right femoral sheath (peripheral specimen) and both IPSs. CRH is then administered peripherally. Repeat ACTH sampling from the periphery and both IPSs is obtained 3 minutes, 5 minutes, 10 minutes, and 15 minutes after the injection of CRH. Samples are collected in tubes that are placed on ice before transport to the laboratory. Upon completion of sampling, both femoral sheaths are removed, and manual compression is used to obtain hemostasis before transferring patients to the recovery room for a rest of approximately 4 hours.

Case series

Pereira et al. evaluated all patients that undergone bilateral inferior petrosal sinus sampling in a tertiary center, between January 1995 and March 2018. The probable diagnosis of Cushing's disease was made when the basal central/peripheral gradient was>2 and/or>3 after stimulation with a corticotrophin-releasing hormone. The localization was suggested when the inter-sinus gradient

was>1.4. The results obtained were compared with the post-operatory results: compatible histology and positive immunohistochemistry to adrenocorticotrophic hormone and/or the presence of criteria of cure. Sensitivity, specificity and predictive positive value were calculated.

A total of 49 patients were evaluated (75.5% female; mean age 45.4 ± 16.3 years old). Bilateral inferior petrosal sinus sampling was compatible with Cushing's disease in 27 out of 28 confirmed cases in histology or by criteria of cure, and was compatible with ectopic secretion in the 2 cases confirmed as ectopic secretion of adrenocorticotrophic hormone (sensitivity 96.4%; specificity 100%). The lateralization calculated was concordant with the results after surgery in 17 out of 27 patients with Cushing's disease - predictive positive value of 63%. Magnetic resonance had a higher predictive value to lateralization - 70.0%.

Bilateral inferior petrosal sinus sampling is a safe and reliable procedure to diagnose Cushing's disease, with great sensitivity and specificity. Nevertheless, the capacity of this procedure to lateralize the lesion inside the pituitary is limited ⁶⁾.

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