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OPINION

Inferior petrosal sinus sampling: Pros and cons; when and where

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The differential diagnosis of Cushing's syndrome has generated more diagnostic tests, more controversy, and more passionate debate than nearly any subject in clinical endocrinology. The introduction of pituitary surgery as the treatment of choice for Cushing's disease, the absence of abnormalities on pituitary imaging studies in many patients with the disorder, and the recognition that some patients with non-pituitary (ectopic) ACTH-secreting neoplasms have endogenous hypercortisolism many years before their tumor becomes clinically apparent, has created a need for a precise differential diagnosis. Before considering whether any diagnostic study should be done, endocrinologists must remember that the pre-test probability of Cushing's disease is at least 90%. In addition, it has been shown that a simple logistic model of clinical variables including the patient's gender, age, approximate duration of symptoms, urine free cortisol, plasma potassium, and plasma ACTH will yield a diagnostic sensitivity of 95-98% for Cushing's disease (1). Therefore, the clinician must compare the diagnostic sensitivity, specificity, and accuracy of any test used in the differential diagnosis of Cushing's syndrome with the use of common sense and the recognition that the majority of patients with ACTH-dependent Cushing's syndrome will have a corticotroph adenoma.

In many medical centers around the world, bilateral simultaneous inferior petrosal sinus ACTH sampling (IPSS) has emerged as the most accurate and reliable means of distinguishing pituitary from non-pituitary ACTH-dependent Cushing's syndrome (25). The major advantage of this procedure is that it is the only diagnostic study that has been reported to yield a diagnostic sensitivity, specificity, and accuracy that is substantially better than the pre-test probability of Cushing's disease. IPSS has been used to help with pre-operative localization of pituitary microadenoma and has been reported to provide accurate localization in 75-90% of patients (3-5). Recently, it has been shown that accurate localization of a pituitary lesion occurred more frequently when based on IPSS results than on imaging results (70% *vs* 49%, respectively). In fact, in patients with discrepant results, IPSS was more likely than pituitary imaging to agree with the final pathological findings (62% *vs* 13%, respectively) (5). Investigators have suggested that sampling directly from the cavernous sinuses rather than from the inferior petrosal sinus may provide even further diagnostic accuracy and improved localization (6). However, some investigators have shown that cavernous sinus sampling actually yields a false negative rate of 20% (7). The lateralization data appears to be approximately 85-90% accurate with cavernous sinus ACTH sampling - really no improvement over bilateral IPSS. Even bilateral sampling from the jugular vein with CRH administration has also been reported as another means of distinguishing pituitary from non-pituitary ACTH-dependent Cushing's syndrome; however, this procedure yields only 80% sensitivity for Cushing's disease and, obviously, provides no information about the site of the microadenoma (8).

Although the diagnostic sensitivity, specificity, and accuracy of IPSS approaches 100% in some clinical centers, results from a recent large scale retrospective multicenter study demonstrated that the overall sensitivity, specificity, and accuracy of IPSS was in the 80-90% range (9). IPSS has also been associated with morbid and even fatal complications including deep vein thrombosis, pulmonary emboli, and brain stem vascular damage (10, 11). However, in a recent series of 166 patients done at an experienced center, IPSS was associated with only one episode of a transient neurological event (sixth nerve palsy) and there were no cases of pulmonary thromboembolism (12).

In addition, IPSS has other potential pitfalls. The

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procedure must be performed when peripheral cortisol levels are elevated in order to suppress the normal corticotroph population of the anterior pituitary. False positive IPSS results for Cushing's disease have been described in two patients who were subsequently found to have ectopic ACTH-secreting tumors (13). Both of these patients had eucortisolemia at the time of the procedure resulting in a misdiagnosis and unnecessary pituitary operation. Currently, our practice is to obtain a late night salivary cortisol level prior to the procedure to ensure that the patients are hypercortisolemic at the time of IPSS (14). Another potential problem with IPSS is the ectopic CRH syndrome. An increasing number of reports has described non-pituitary neoplasms secreting CRH and often ACTH concomitantly (15). If ectopic CRH predominates from these tumors, a "false positive" IPSS may be seen. Therefore, we also obtain a peripheral CRH measurement in all patients undergoing IPSS.

These differences in diagnostic utility and complication rates from IPSS can only be explained by differences in the skills of the invasive radiologist performing the procedures. Since inferior petrosal sinus ACTH sampling is a technical procedure, some physicians (particularly those with extensive experience) will have better results and fewer complications. Physical genius is not conferred evenly (16). For example, the Italian mens' soccer team is technically superior to the one from the United States even though they both play with the same ball on the same field and with the same rules. Life would be very boring if it were any other way.

When and where should inferior petrosal sinus sampling be performed in patients with ACTH-dependent hypercortisolism? In the presence of an unequivocal pituitary lesion (≥5 mm), a patient with the typical clinical presentation of Cushing's disease can be usually referred to pituitary surgery without further testing. In the absence of a pituitary or non-pituitary tumor, IPSS with CRH stimulation should be performed in order to secure the diagnosis of Cushing's disease and hopefully localize the corticotroph adenoma. IPSS should be done in experienced and dedicated centers (5-10 procedures per year) where there is an established track record and a proven diagnostic accuracy of close to 100%. Obviously, if the sensitivity, specificity, and diagnostic accuracy of IPSS is less than the pre-test probability of Cushing's disease, the procedure cannot be justified. Finally, endocrinologists, regardless of where they practice, must realize that none of the vast array of diagnostic tests for Cushing's syndrome should replace clinical experience and good common sense.

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