



Pituitary magnetic resonance imaging vs. bilateral inferior petrosal sinus sampling: comparison between non-invasive and invasive diagnostic techniques for Cushing's disease—a narrative review

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Abstract: Cushing's syndrome is a pathological clinical condition caused by an exposure of elevated cortisol levels over a long period of time. It is therefore essential to establish what the cause of hypercortisolism is. In most cases (about 80%) the pathological process is due to adrenocorticotrophic hormone (ACTH), while in a minor part of the cases (about 20%) the cause is represented by a pathology of the adrenal glands and therefore not related to ACTH. Most patients with ACTH dependent Cushing's syndrome have a pituitary microadenoma; in the remaining cases (30%), the high level of cortisol is linked to an ectopic secretion of ACTH. Surgical removal of the pituitary adenoma represents the treatment of choice in Cushing's disease (CD) patients; it is therefore necessary to identify and precisely locate the pituitary tumour responsible for the secretion of ACTH. Adequate diagnostic information is very often, even with magnetic resonance imaging (MRI), and in these cases we rely on bilateral inferior petrosal sinuses sampling (BIPSS). This procedure is considered the gold standard method for the diagnosis, but like any other diagnostic method it is not free from erroneous results such as false positives or false negatives.

Keywords: Cushing's disease (CD); magnetic resonance imaging (MRI); bilateral inferior petrosal sinus samples; microcatheter

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Introduction

Cushing's syndrome is a clinical condition resulting after long-standing exposure to elevated levels of glucocorticoids (1). One of the main diagnostic challenges

is identifying the underlying cause of hypercortisolism. In approximately 80% of cases, the cause is an adrenocorticotrophic hormone (ACTH)-dependent process; in approximately 20% of cases the hypercortisolism is related to primary adrenal causes (that is, ACTH

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independent) (2). Most of the ACTH-dependent cases (approximately 70% of all cases) are due to a pituitary adenoma [Cushing's disease (CD)]; in the remaining cases, the hypercortisolism is secondary to an ectopic ACTH secretion (1,3). Surgical removal of the pituitary adenoma is the treatment of choice in patients with CD. Thus, localization of the source of ACTH secretion is critical in guiding timely treatment decisions. Exposure to elevated cortisol levels over a long period of time causes a very serious clinical pathological syndrome represented by Cushing's syndrome (1). Therefore the main diagnostic challenge to reach the most suitable therapeutic solution is to discover the cause of hypercortisolism. Pituitary adenoma is responsible for CD in most cases (about 70% of all cases) while the ectopic secretion of ACTH represents the cause of hypercortisolism in the remaining part (1,3). The treatment of choice is the surgical removal of adenoma. It is therefore necessary to locate and identify the source of ACTH secretion to plan the treatment. We present the following article in accordance with the NARRATIVE REVIEW reporting checklist (available at <http://dx.doi.org/10.21037/gs-20-654>).

Magnetic resonance imaging and its rule in the diagnostic workup

The diagnostic method of choice for the diagnosis of CD is currently represented by magnetic resonance imaging (MRI) (4,5). In the case of the suspicion of an ACTH secreting pituitary tumour, it is advisable to use a specific MRI study both in clinical practice and in pharmacological trials. MRI examination must be performed with a scanner of at least 1.5 Tesla with the use of coronal and sagittal T1-weighted spin-echo (SE) sequences before and after intravenous administration of gadolinium contrast medium and with T2-weighted sequence on the coronal plane, in order to obtain an optimal diagnostic level. High spatial detail is necessary. Thin sections (with a thickness of 2–3 mm or smaller), a fine matrix size (256×512 or more) and a small field of view (FOV) (6) become fundamental technical parameters. A FOV focused on the pituitary region must be used to detect a microadenoma because, with the same matrix, a larger FOV offers a lower diagnostic resolution. In fact, a pituitary study conducted with a 12 cm × 12 cm FOV has a higher resolution than a study conducted with an 18 cm × 18 cm FOV, for the same matrix (7). A repetition time (TR) in the range of 500–700 ms and an Echo Time (TE) in the range of 15–

25 ms represent other important technical parameters (6), although better results have been obtained with shorter TR (400 ms) and TE (10.3 ms) (7). The use of the dynamic technique, with multiple coronal sequences after intravenous gadolinium injection, allows to achieve high sensitivity and specificity. A pituitary lesion can be found with this technique in 96% of patients with a biochemical diagnosis of ACTH-dependent CD (8), while in suspected CD patients a pituitary lesion can be identified with a 50–60% higher diagnostic sensitivity rate than that reported in non-dynamic MRI. Moreover other technical factors are sagittal and coronal T1-w fat saturated post gadolinium sequences in order to better delineate the pituitary lesions in the postoperative follow up (9). The diagnostic sensitivity of an MRI study is also affected by the dose of contrast medium. The recommended dose of paramagnetic contrast medium for most intracranial lesions is 0.1 mmol/kg (10), but a 50% reduction of the usual dose of contrast medium can be used without a significant loss of sensitivity as described in many studies performed both on pituitary tumour and in normal gland (11,12). However, there are limited and unclear data (13–16). The signal-to-noise ratio is essential to ensure adequate diagnostic value of an MRI exam. It is calculated from the difference in signal strength between the area of interest and the background and determines the graininess of the image. The grainier the image, the lower the signal-to-noise ratio. We can obtain an increase in the signal-to-noise ratio with the use of a three-dimensional (3D) acquisition with very thin sections (up to 1 mm) (17), as for example with the MRI technique based on the use of 3D spoiled gradient recalled acquisition in the steady state (SPGR) sequence. This sequence allows to obtain a higher soft tissue contrast than the T1-w SE technique. Spatial resolution in MRI can be increased by two methods: (I) acquiring more data and signal averaging but with a longer acquisition time and thus increasing possible motion artifacts; (II) increasing the intensity of the magnetic field (18). The 3 Tesla operating machines allow MRI exams to be performed with greater spatial resolution with reduced acquisition time thanks to the high MR signal and offer many advantages for the identification of pituitary tumors (19). In particular, the 3 Tesla MRI allows a better identification of the pituitary microadenomas and a greater anatomical detail for the study of the parasellar region, useful for evaluating possible invasion of the cavernous sinus (20,21). This is made possible thanks to the use of 3D T1-w sequences with a reduced slice thickness (1–2 mm), which allows to obtain high quality images while

minimizing susceptibility artifacts in the sellar and parasellar regions (22,23). However, high-field imaging is not free from artifacts. The base of the skull as sellar and parasellar regions are susceptible to artifacts due to the interface of soft tissues, air and bones, which can be reduced with the use of three-dimensional fast SE (FSE) techniques. Despite the high magnetic field intensity and the various technical measures to reduce the artifacts, the identification of the secreting ACTH pituitary adenomas is still very difficult. In fact, in several case series involving adult patients, only 40–50% of pituitary adenomas were detected (24,25). The identification of a pituitary lesion especially if less than 5 mm does not mean, however, to have found a pituitary adenoma responsible for a clinical symptomatology since a part of the general population between 10% and 20% has a pituitary incidentaloma (25,26). In a recent meta-analysis (27), an overall prevalence of pituitary adenomas of 16.7% was found (14.4% in autopsy studies and 22.5% in imaging studies). For this reason it is very important to prove with further clinical instrumental evidence the presence of a pathological secretion of ACTH by the pituitary gland.

Inferior petrosal sinus sampling and its rule in the diagnostic workup

In the event that the results of clinical, biochemical and radiologic tests are equivocal or discordant, bilateral sampling of the inferior petrosal sinuses (IPSS) must be performed to confirm the presence of a secreting ACTH pituitary adenoma (28). Bilateral IPSS was introduced for the first time in the early 1980s (29,30). Subsequently, its use with and without corticotropin releasing hormone (CRH) administration was described in order to solve problems of differential diagnosis of Cushing's syndrome (31,32). In this technique the operator inserts the sheaths bilaterally through the femoral veins. They are then advanced through the internal jugular veins into the lower petrosal sinuses.

Blood samples are taken from each sinus, obtaining them simultaneously, from both central catheters and the peripheral vein, to be able to compare plasma ACTH levels with each other. Serial samples are taken before and after administration of CRH (1 mg/kg body weight). In CD, a central to peripheral (central/peripheral) ACTH gradient results from high levels of ACTH in the venous drainage from the pituitary gland, whereas in the case of an ectopic ACTH secretion gradient it is not identified. A baseline ratio of central/peripheral ACTH values of 2.0 or greater

is indicative of CD in case of non-administration of CRH (33). Since ACTH secretion is episodic and sampling can miss the burst of ACTH secretion, CRH is used as a stimulating agent to increase sensitivity, by collecting ACTH plasma samples from both inferior petrosal sinuses and peripherally at intervals after CRH administration. A central/peripheral ACTH ratio of 3.0 or higher suggests CD (31). Most patients with ectopic ACTH secretion exhibit a central/peripheral ACTH ratio of less than 2.0 before and after CRH administration (33). To obtain a valid IPSS study, there must be correct cannulation of the inferior petrosal sinuses. For this reason, it is recommended to perform checks with digital subtraction angiography to verify the correct positioning of the catheter and to correctly evaluate the venous anatomy (*Figure 1*). IPSS has high accuracy and efficiency in the diagnosis of Cushing's syndrome in experienced institutions, allowing to reach, for example, a sensitivity of 96% and a specificity of 100% in a recent meta-analysis of 21 researches, while thanks to the CRH stimulation the sensitivity can increase to 100% (34,35). In another study (36) the sensitivity for IPSS was 82% while it was 48% for the high dose dexamethasone test and 70% for the CRH test. When compared with other imaging modalities, IPSS showed a high accuracy: in a study performed on 54 patients (37) the accuracy of IPSS was 88% while the accuracy of MRI was 54%; in another study where 84 patients were enrolled, the sensitivity was 40% for CT (38,39), 50% for MRI and 90% for IPSS (40). The diagnostic accuracy of MRI in differentiating central and ectopic Cushing's syndrome was found to be 58% while the accuracy of IPSS was found to be 100% (35). Several studies showed, however, that the diagnostic accuracy is not absolute and both false-negatives (lack of a central/peripheral gradient in patients with CD) and false positives (presence of a central/peripheral gradient in patients with ectopic ACTH secretion) occur. False negatives may occur in 10–15% of patients, with a higher prevalence on baseline, unstimulated ACTH levels (41). These patients usually present unilateral or bilateral anatomical variants in the petrosal venous system. Originally four variants were classified (42): the most common variant (Type I), being the petrosal sinus draining directly into the internal jugular vein (*Figure 2*). This classification was further modified and the most recent version describes six variants, with emphasis on the petrosal-jugular junction (43,44). All these variants result in a success rate of less than 100% of bilateral petrosal cannulation and sampling (45). In a large

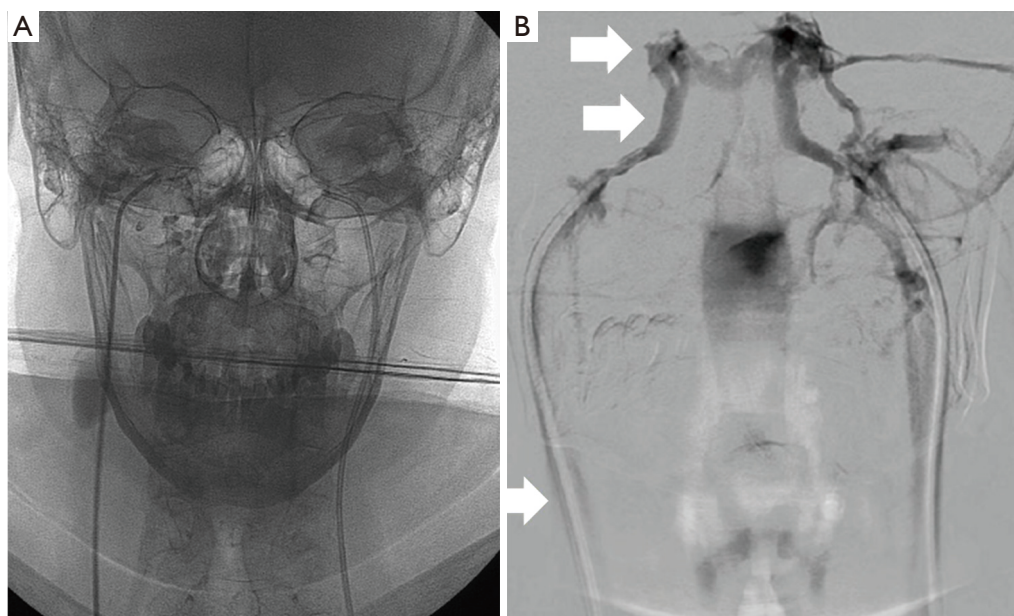


Figure 1 Inferior petrosal sinuses venography. (A) Well positioned catheters within the inferior petrosal sinuses. (B) Inferior petrosal sinuses venography during contrast medium injection. The white arrows indicate the inferior petrosal sinus draining directly into the internal jugular vein.

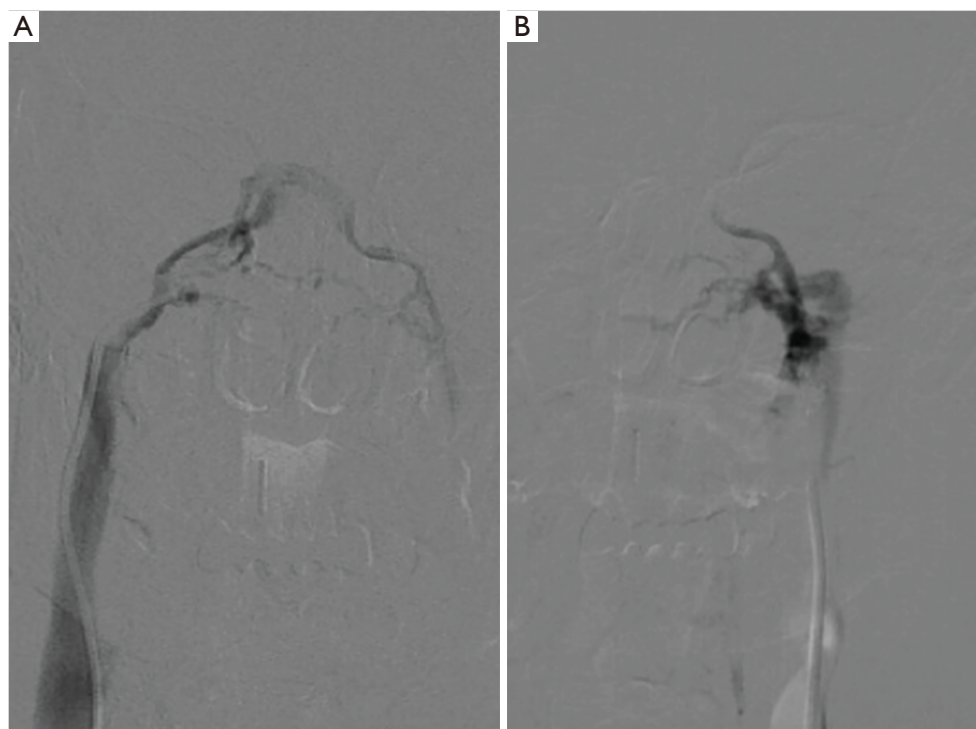


Figure 2 Patient with the initial diagnosis of Cushing's disease, in whom MRI showed no pituitary lesions. (A,B) Inferior petrosal sinus sampling found bilateral Type 1 drainage and a right-sided lateralization. Transsphenoidal right tumorectomy confirmed the presence of a pituitary adenoma.

series (501 patients) (46) the false negatives obtained in 0.8% of the patients were due to a hypoplastic or abnormal inferior petrosal sinus. The variability in the tumoral corticotrope secretory pattern can also determine false-negative results (45) and the secretion of ACTH by the adenoma in the petrosal sinuses at some time may not even reach a level 2 or 3 times higher than its peripheral serum concentration as usually expected. In patients with intermittent ectopic ACTH secretion there may be periods of time when cortisol levels are normal. Performing IPSS in such periods can lead to ambiguous results. False positives can also be caused by tumours that secrete CRH (47). Efforts to improve the diagnostic accuracy include additional sampling during IPSS for other anterior pituitary hormones, including prolactin for normalization of ACTH ratios. Since the inter-sinus ratio ACTH is known to be correct in less than 70% of cases, the inter-sinus ratio of prolactin has been used to identify the tumor site in the pituitary gland (48,49). However, even with the use of this correct ACTH ratio for prolactin, the prediction of the tumour site sometimes remains uncertain (50). Higher diagnostic sensitivity may be achieved if IPSS is performed after stimulation with CRH. However, it is not readily available all over the world and then an alternative stimulating factor represented by desmopressin, more easily available, has been used (51,52), obtaining excellent results over the years. About 150 patients with CD tested with desmopressin have so far been reported (53–55) showing a sensitivity comparable to that of stimulation with CRH (i.e., 90–97%). The combined stimulation with the administration of both desmopressin and CRH together, performed to amplify the corticotropic responses, identified a central/peripheral ACTH gradient in 46 out of 47 patients with CD (56). However, the use of desmopressin is not free from serious complications since this agent is a known hemostatic and causes the release of von Willebrand factor and other factors of the coagulation cascade, which in a patient with CD could cause serious side effects (53). Bilateral IPSS is a reliable method if performed by an experienced interventional radiologist (57). The most common complication is the venous access site hematoma which can be seen in 3–4% of patients (58). Serious complications are very rare. Pontine hemorrhage and vasovagal reactions as serious neurological complications have been reported in a large series of 508 patients. In the same series, minor and temporary complications such as dizziness and paraesthesia have been reported in three patients. In a different case report, the

same authors reported medial medullary syndrome in a patient who developed non-hemorrhagic right medullary infarct site (58). Temporary 6th nerve palsy has been reported in two patients in a study of 86 patients (59). In a series of 94 patients, one patient suffered from venous subarachnoid hemorrhage resulting in acute obstructive hydrocephalus (60). In another series of 44 patients, brain stem infarct was detected by MRI in a patient (61). These complications are very rare and usually related to catheter selection and mapping or variations in venous anatomy. IPSS-related thromboembolic complications have also been reported. Since patients with Cushing's syndrome are predisposed to states of blood hypercoagulability, prophylactic heparinization during the procedure is very important (62,63); 2 of 43 patients were reported to develop deep vein thrombosis after IPSS, causing pulmonary thromboembolism in one of them; however, it was stated that no prophylactic heparinization was conducted (64). Deep vein thrombosis was documented in one of the 94 patients in another study, too (65). In our experience we have always subjected patients to prophylactic heparinization treatment without ever having encountered similar complications during and after the procedure. However, IPSS is a difficult procedure that requires technical mastery gained over the years. This led to look for simpler ways, such as jugular vein sampling. By comparing both methods, the sensitivity of jugular venous sampling was reported as 80% and IPSS as 95% (66). Another group reported the sensitivities of jugular venous sampling as 83% and IPSS as 94% (67). Although erroneous results need to be re-evaluated using IPSS, the jugular venous sampling can be used as an alternative procedure in institutions with limited technical experience, as we can read in these studies. An alternative to IPSS can be the cavernous sinus sampling (68). This technique would provide adequate and optimal central/peripheral ACTH gradients without even the administration of CRH since the cavernous sinuses are closer to the pituitary gland. It can be useful for identifying lateralization, but currently it is performed only by a limited number of neuroradiologists. During this procedure, technically similar to IPSS, the tip of the catheter is extended adjacent to the cavernous sinus. The position of the catheter is verified by venography of the cavernous sinus, performed by manual injection and with a minimal amount of contrast material in order to avoid complications, such as cerebral infarction and venous thrombosis. This superselective cavernous sinus sampling provided an accurate localization

of the functional lesion in 73.3% without CRH stimulation and 93.3% with CRH stimulation (66,68). Although this procedure can be considered an important additional tool in guiding lateralization its use is currently not routine given its increased invasiveness and potentially increased risk of neurological complications (59).

Prospective studies with larger patient groups are required (58).

Conclusions

IPSS is an accurate and safe invasive diagnostic method in expert hands and plays an important role within the decisional algorithm for diagnosis and management of the Cushing syndrome.

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