

Venous Angiography Is Needed to Interpret Inferior Petrosal Sinus and Cavernous Sinus Sampling Data for Lateralizing Adrenocorticotropin-Secreting Adenomas

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ABSTRACT

Bilateral simultaneous venous sampling of ACTH from the inferior petrosal sinus is a reliable test for diagnosing Cushing's disease, but is not reliable for lateralizing ACTH-secreting pituitary adenomas. We reviewed 23 consecutive patients with Cushing's disease who underwent venous angiography of the cavernous and inferior petrosal sinuses followed by bilateral simultaneous venous sampling of ACTH in the inferior petrosal and cavernous sinuses. Venous drainage was bilaterally symmetric in 14 patients (61%) and asymmetric in 9 (39%). The most common asymmetric pattern (6 patients) was for blood from both cavernous sinuses to drain into the right inferior petrosal sinus, with no significant drainage into the left. Cavernous sinus sampling in 21 patients correctly lateralized the tumor in 12 cases of symmetric

venous drainage, but in only 3 cases of asymmetric drainage. Inferior petrosal sinus sampling in all 23 patients correctly lateralized the tumor in 12 cases of symmetric drainage, but in only four cases of asymmetric drainage. Overall, venous sampling correctly lateralized 70% of the tumors. Incorrect lateralization in cases of asymmetric venous drainage is probably attributable to shunting of blood toward the side of dominant venous drainage. Our findings illustrate the need for venography in all patients undergoing venous sampling of ACTH because an understanding of the venous drainage patterns is essential to correctly interpret venous sampling data and warn physicians that the lateralization data may be incorrect or unreliable. (*J Clin Endocrinol Metab* 81: 475-481, 1996)

INFERIOR petrosal sinus sampling of ACTH, either with or without CRH stimulation, is routinely used to differentiate Cushing's disease from other forms of chronic hypercortisolism, especially ectopic ACTH syndrome. With a diagnostic accuracy of 90-100% in most recent series (1-11), inferior petrosal sinus sampling is generally considered the most accurate way to establish a diagnosis of Cushing's disease. Bilateral simultaneous sampling of the inferior petrosal sinuses has also been used preoperatively to localize ACTH-secreting pituitary adenomas, but does so correctly in only 47-68% of cases (1, 6-18). Accurate lateralization is important because most ACTH-secreting pituitary adenomas cannot be detected by magnetic resonance (MR) imaging (19, 20), and surgical resection is the most effective treatment for Cushing's disease (8). If the lateralization data are convincing, but no discrete tumor can be identified during surgery, some surgeons will proceed with partial or total hypophysectomy. Incorrect lateralization data can have devastating consequences in these situations.

In light of the potential difficulties encountered in lateralizing an ACTH-secreting tumor by bilateral simultaneous venous sinus sampling, it is important to understand the limitations of this technique and the options available for improving its diagnostic accuracy. We, therefore, reviewed

a series of consecutive patients with Cushing's disease in whom venograms performed before venous sampling demonstrated various patterns of venous drainage. In this report, we analyze the relation venous drainage patterns, the venous sampling (lateralization) data, and the operative and pathological findings. The goal of the study was to determine whether identifying the pattern of venous drainage is essential for proper interpretation of venous sampling data.

Subjects and Methods

Patients

The records of all patients who underwent bilateral simultaneous venous sampling of ACTH and subsequent transsphenoidal surgery for Cushing's disease at the University of California-San Francisco (UCSF), between January 1, 1993, and December 31, 1994, were retrospectively reviewed. This 2-yr period was selected because since late 1992 all patients with suspected Cushing's disease have undergone venography of the cavernous and inferior petrosal sinuses, followed by bilateral simultaneous sampling without CRH stimulation. Patients in whom venous sampling data showed evidence of Cushing's disease then underwent transsphenoidal exploration of the pituitary gland by a single surgeon (C.B.W.) with extensive experience in surgery for Cushing's disease (8). To assess the utility of venography in interpreting the results of venous sampling of ACTH and its relation to clinical outcome, we reviewed the venograms, venous sampling data, and the operative and pathological findings.

Venous sampling

Venous sampling was performed on an out-patient basis without heparinization by the Neurointerventional Radiology Service, UCSF, as previously described (21). All procedures were performed by operators

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with extensive experience in venous phase angiography. Bilateral 7.0 Berenstein catheters were guided transfemorally into the proximal jugular veins, and HiFlow Tracker microcatheters (Target Therapeutics, San Jose, CA) were then advanced into the cavernous sinuses under fluoroscopic guidance. Antero-posterior and lateral venous angiograms (venograms) were obtained after manual injection of 1 mL contrast material. Conventional angiography was then performed. Because the cavernous sinus and inferior petrosal sinus are a low pressure venous system, care was taken to try to ensure that the manual injections did not overwhelm or alter flow patterns, and that the pressure or time of injection was uniform bilaterally. Lateral projection venograms helped to clearly define the junction between the cavernous sinus and inferior petrosal sinus, and define the full extent of these structures, whereas antero-posterior venograms were used to interpret venous drainage patterns. After the venous drainage of the cavernous and inferior petrosal sinuses was defined, bilateral simultaneous venous sampling was performed over 10 min, first in the cavernous sinuses and then in the high, middle, and low inferior petrosal sinuses, jugular bulbs, innominate veins, superior and inferior vena cavae, and femoral veins. Before each sampling, catheter tip position was confirmed fluoroscopically. Multiple sites in the cavernous and inferior petrosal sinuses were sampled to attempt to reduce variability in ACTH levels attributable to slight variations in catheter placements and size of the venous sinuses. Femoral venous ACTH values were taken as a measure of peripheral ACTH concentration. ACTH was determined in blood from the jugular or innominate veins and vena cavae to distinguish ectopic ACTH secretion from true Cushing's disease. The blood samples were processed, and ACTH levels were measured by RIA (4).

A central (measured at the cavernous sinus or inferior petrosal sinus) to peripheral ACTH ratio greater than 2:1 was required to establish a diagnosis of Cushing's disease. A lateralizing gradient (right *vs.* left cavernous or inferior petrosal sinus) greater than 2:1 was considered a reliable predictor of tumor lateralization within the pituitary gland. Venous sampling was considered to lateralize a tumor correctly when the lateralization gradient was toward the side on which the tumor was identified pathologically. A 1:1 gradient (*i.e.* equal ACTH concentration bilaterally) was considered accurate if no tumor was found after total hypophysectomy or if a midline tumor was identified.

Surgical management

All patients received extensive preoperative counseling regarding the possibility that hemi- or total hypophysectomy might be performed if no discrete tumor could be identified. Informed consent was obtained from each patient.

Final decisions regarding surgical resection were made at the surgeon's discretion at the time of surgery. In general, a hemihypophysectomy was performed if no discrete adenoma could be identified after a meticulous bilateral exploration and if venous sampling demonstrated a lateralizing gradient greater than 2:1. A total hypophysectomy was performed only if venous sampling unequivocally demonstrated Cushing's disease (central-peripheral ACTH ratio >2:1), no lateralizing gradient was identified, the patient's health was greatly endangered by symptoms of chronic hypercortisolism, and the patient's full growth potential and pubescent development had been achieved. No patient in this series underwent bilateral adrenalectomy as an alternative to total hypophysectomy, although, in general, this is considered an option in patients with negative surgical explorations. All pathological specimens were stained by the immunoperoxidase method for ACTH, GH, and PRL and reviewed by the Neuropathology Unit, UCSF. If pathological studies demonstrated an adenoma, or if no adenoma was identified but hormonal assays for cortisol and the clinical course were consistent with the remission of Cushing's disease, surgery was considered successful.

Assessment of venograms

Venograms were retrospectively reviewed to identify anomalies and asymmetric drainage patterns. Venous anatomy was considered symmetric if both cavernous and inferior petrosal sinuses were patent, filled from a unilateral injection of contrast material, and drained primarily into the inferior petrosal sinus ipsilateral to the site of injection. Drainage was also considered symmetric if cross-filling of the contralateral cavernous sinus and inferior petrosal sinus occurred bilaterally and on

roughly equal proportions on both sides. All other patterns of drainage were classified as asymmetric.

Statistical methods

The Mann-Whitney U test was used for statistical comparison of ACTH values and lateralizing gradients obtained from the cavernous sinus and inferior petrosal sinus. Fisher's exact test was used to assess the interaction between the accuracy of lateralizing gradients and venous drainage patterns; $P < 0.05$ was considered statistically significant. All statistical analyses were performed with InStat (GraphPad) statistical software.

Results

During the 2-yr review period, 25 patients with suspected Cushing's disease underwent bilateral simultaneous venous sampling of ACTH from the cavernous and inferior petrosal sinuses; no complications were reported in any of the patients. Cushing's disease was diagnosed in 23 of these patients, based on a central to peripheral ACTH ratio greater than 2:1; two patients were found to have ectopic ACTH-secreting tumors. The clinical, radiographic, and operative findings in these patients are summarized in Table 1. There were 16 females and 7 males, ranging in age from 12–69 yr.

Venography

Both cavernous sinuses were successfully catheterized in 21 patients. In two patients (no. 12 and 14), occlusion of the middle or high inferior petrosal sinus prevented access to the cavernous sinus on 1 side. Venous drainage was symmetric in 14 patients (61%). In these patients, the cavernous and inferior petrosal sinuses typically drained ipsilateral to the side of filling, with minimal cross-filling of the contralateral side (Fig. 1); significant but symmetric bilateral cross-filling was noted in only 1 patient.

Venous drainage was asymmetric in 9 patients (39%). Seven patients had right side-dominant drainage, in which both cavernous sinuses drained almost exclusively through the right side even though both sides were patent (Fig. 2). Two patients had left side-dominant drainage, one with significant outflow through an enlarged left superior ophthalmic vein (Fig. 3). In the one patient with an occluded right inferior petrosal sinus (no. 12), both cavernous sinuses drained through the left cavernous sinus and left inferior petrosal sinus. No other asymmetric patterns were noted.

Venous sampling

Bilateral venous sampling of ACTH from the inferior petrosal sinuses was performed in 23 cases. In 1 patient (no. 12), blockage of the midportion of the right inferior petrosal sinus prevented cavernous sinus and high inferior petrosal sinus sampling on that side. A lateralizing gradient of 2:1 or greater was found in 16 patients by cavernous sinus sampling and in 22 by inferior petrosal sinus sampling. In 13 patients, the lateralizing gradient was concordant between samples from the 2 sinuses. In 4 patients (no. 5, 6, 16, and 18), inferior petrosal sinus sampling demonstrated a lateralizing gradient, whereas cavernous sinus sampling did not. In 2 of these subjects (no. 5 and 6) the central to peripheral ACTH ratio ipsilateral and contralateral to the tumor was less than 2:1; this ratio was more than 2:1 in the other subjects (no. 16

TABLE 1. Summary of venous drainage patterns, venous sampling ACTH lateralizing gradients, operative findings, pathological results, and outcome

Patient no.	Age (yr)	Sex	Venous drainage pattern	Inferior		Operative findings	Procedure	Pathology	Outcome
				Cavernous sinus gradient (lateralization)	petrosal sinus gradient (lateralization)				
1	53	M	Symmetric	7:1 (right)	6:1 (right)	No tumor identified	Right hemihypophysectomy	ACTH adenoma	Remission
2	26	F	Symmetric	15:1 (left)	13:1 (left)	Left adenoma (1 mm)	Focal resection	ACTH adenoma	Remission
3	50	F	Symmetric	7:1 (left)	9:1 (right)	Left adenoma (6 mm)	Focal resection	ACTH adenoma	Remission
4	25	M	Symmetric	1:1	1:1	Midline adenoma (1 mm)	Focal resection	ACTH adenoma	Remission
5	27	M	Symmetric	1:1	4:1 (right)	No tumor identified	Right hemihypophysectomy	ACTH adenoma	Remission
6	58	M	Symmetric	1:1	14:1 (right)	No tumor identified	Right hemihypophysectomy	ACTH adenoma	Remission
7	22	F	Right side dominant	2:1 (right)	4:1 (right)	No tumor identified	Right hemihypophysectomy	No tumor	Persistent Cushing's disease
8	40	F	Symmetric	2:1 (right)	3:1 (right)	No tumor identified	Right hemihypophysectomy	No tumor	Remission
9	25	M	Symmetric	7:1 (right)	2:1 (right)	No tumor identified	Right hemihypophysectomy	No tumor	Remission
10	49	F	Right side dominant	2:1 (right)	3:1 (right)	No tumor identified	Total hypophysectomy	GH staining, no ACTH positive cells	Remission
11	43	F	Left side dominant, significant drainage via superior ophthalmic vein	3:1 (left)	8:1 (left)	Left adenoma (2 mm)	Focal resection	ACTH adenoma	Remission
12	43	F	Right inferior petrosal sinus occluded 3 mm above jugular bulb; left side dominant	Not done	2:1 (right)	Right adenoma (2 mm)	Focal resection	ACTH adenoma	Remission
13	36	F	Symmetric	3:1 (left)	5:1 (right)	Left adenoma (near midline) (3 mm)	Focal resection	ACTH adenoma	Remission
14	29	F	Occluded left cavernous sinus; right-dominant drainage	Not done	4:1 (right)	Left adenoma (intracavernous)	Focal resection	ACTH adenoma	Remission
15	46	F	Symmetric	21:1 (right)	7:1 (right)	No tumor identified	Right hemihypophysectomy	No tumor	Remission
16	16	M	Right side dominant	1:1	4:1 (right)	Left adenoma (4 mm)	Focal resection	ACTH adenoma	Remission
17	17	F	Symmetric	2:1 (right)	3:1 (right)	No tumor identified	Right hemihypophysectomy	ACTH adenoma	Remission
18	69	F	Right side dominant	1:1	2:1 (right)	Right adenoma (4 mm)	Focal resection	ACTH adenoma	Remission
19	12	M	Right side dominant	28:1 (left)	4:1 (right)	Left adenoma (2 mm)	Focal resection	ACTH adenoma	Remission
20	43	F	Symmetric	7:1 (right)	6:1 (right)	Left adenoma (6 mm)	Focal resection	ACTH adenoma	Remission
21	41	F	Symmetric	28:1 (left)	4:1 (left)	Right adenoma (?)	Focal resection	ACTH adenoma	Remission
22	54	F	Symmetric	12:1 (left)	2:1 (left)	Left adenoma (3 mm)	Focal resection	ACTH adenoma	Remission
23	37	F	Right side dominant	4:1 (right)	3:1 (right)	Right adenoma (2 mm)	Focal adenoma	ACTH adenoma	Remission

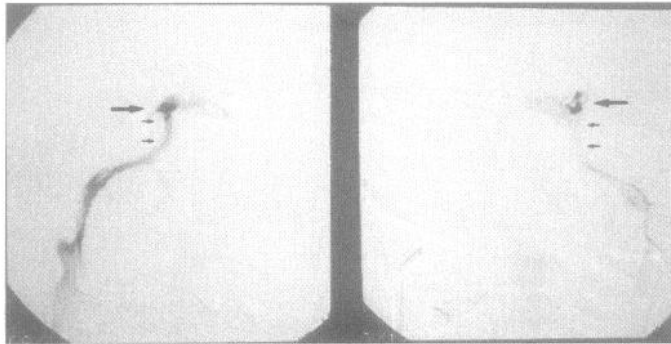


FIG. 1. Symmetric venous drainage pattern. Late phase sinus venograms obtained after the injection of contrast material into the right (A) and left (B) cavernous sinuses. Note the symmetric and predominantly ipsilateral filling and drainage of the cavernous sinus and inferior petrosal sinus, with only trace cross-filling of the contralateral venous system. *Large arrows* indicate the cavernous sinus; *small arrows* indicate the inferior petrosal sinus.

and 18). In 3 patients (no. 3, 13, and 19), cavernous sinus sampling was discordant with inferior petrosal sinus sampling (lateralized to opposite side). A nonlateralizing gradient was found in 5 patients by cavernous sinus and in 1 patient by inferior petrosal sinus sampling.

Operative and pathological findings and clinical outcome

Eighteen patients underwent focal removal of an adenoma that stained positively for ACTH. The tumor was located in the right half of the anterior pituitary gland in eight cases, in the left half in nine cases, and in the midline in one case; all of these patients had clinical remission of their Cushing's disease. A hemihypophysectomy was performed in eight patients, all with right side ACTH gradients; pathological evaluation revealed an adenoma in four of these patients and no tumor in four; seven of these patients were cured of their Cushing's disease. Total hypophysectomy was performed in one patient; immunoperoxidase staining failed to demonstrate an ACTH-secreting adenoma in this patient, but clinical remission of Cushing's disease was achieved.

Cavernous sinus versus inferior petrosal sinus sampling

Cavernous sinus sampling of ACTH correctly lateralized the tumor in 15 of the 21 patients in whom it was performed, whereas inferior petrosal sinus sampling correctly lateralized the tumor in 16 of 23 patients. The mean lateralizing gradient was 7.4:1 for cavernous sinus sampling and 4.2:1 for inferior petrosal sinus sampling. This difference was not statistically significant.

Influence of venous drainage patterns on lateralization gradients

In 12 of 14 patients with symmetric venous drainage, lateralization of the adenoma determined by cavernous sinus sampling agreed with the pathological findings (Table 2). In 5 of these patients, hemihypophysectomy was performed, and clinical remission was achieved. Similarly, inferior petrosal sinus sampling accurately lateralized the tumor in 12 of these 14 patients. Thus, in patients with symmetric venous drainage, cavernous sinus sampling and inferior petrosal

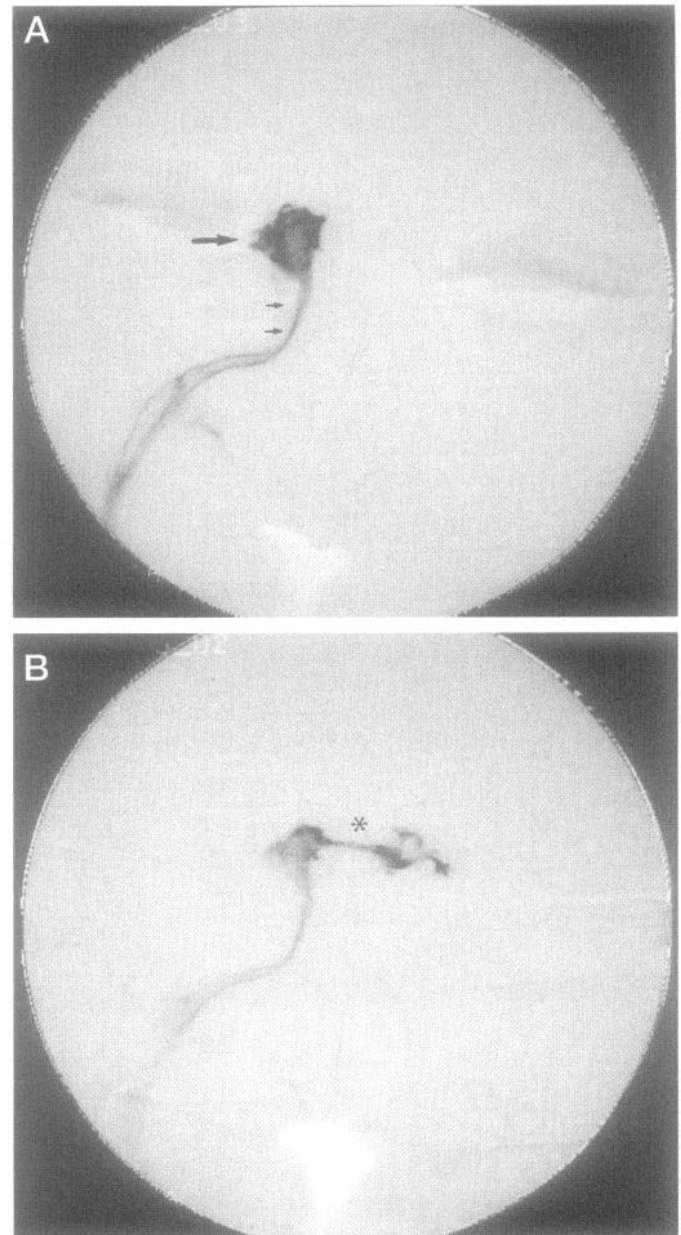


FIG. 2. Right side-dominant venous drainage. A, Late phase venograms obtained after injection of contrast material into the right cavernous sinus (frontal projections) demonstrate filling of the right cavernous sinus and drainage via the right inferior petrosal sinus to the jugular bulb. No drainage of venous blood via the left cavernous sinus and inferior petrosal sinus is noted. B, Late phase venograms obtained after injection of contrast material into the left cavernous sinus (frontal projections). Note the rapid cross-filling of the right cavernous sinus via the circular sinus and drainage via the right inferior petrosal sinus with essentially no left side drainage. *Large arrows* indicate the cavernous sinus; *small arrows* indicate the inferior petrosal sinus; the *asterisk* identifies the circular sinus.

sinus sampling were equally reliable methods, correctly lateralizing the tumor in 86% of cases.

Cavernous sinus sampling could be performed in only seven of the nine patients with asymmetric venous drainage. Cavernous sinus sampling agreed with the pathological findings in only three cases, whereas inferior petrosal sinus sam-

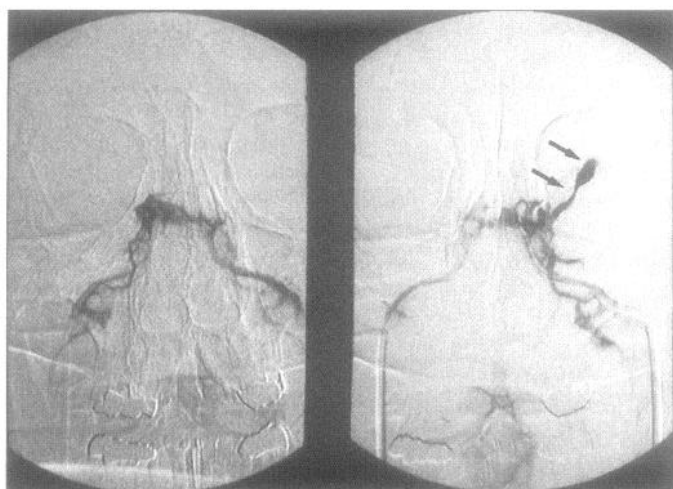


FIG. 3. Left side-dominant venous drainage. Right side (A) and left side (B) late phase venograms demonstrate that the right cavernous sinus drains primarily through the left inferior petrosal sinus, whereas the left cavernous sinus drains primarily through the left inferior petrosal sinus, with minimal drainage through the right inferior petrosal sinus. The arrow points to dilated ophthalmic vein.

pling agreed in four of nine cases. Patients with asymmetric venous drainage tended to have smaller lateralizing venous gradients than those with symmetric drainage (5.6:1 vs. 9.3:1), although this difference was not significant. Thus, cavernous sinus sampling was accurate in 86% of cases in which venous drainage was symmetric, but in only 42% of cases in which venous drainage was asymmetric ($P < 0.11$). Similarly, inferior petrosal sinus sampling was accurate in 86% of cases with symmetric drainage and 44% of cases with asymmetric drainage ($P < 0.16$).

Discussion

In most investigations of the efficacy of inferior petrosal sinus sampling, fluoroscopy is used only to confirm the location of the catheter in the inferior petrosal sinus; complete venograms are not obtained routinely (1-16, 19, 20, 22-24). Consequently, data on asymmetric venous drainage patterns are scarce. Although it is possible that the mixing of venous blood from nonpituitary sources can affect the results of inferior petrosal sinus sampling (14, 17, 23), venographic data have not been considered essential for interpreting the results of inferior petrosal sinus sampling. To our knowledge, this series is the first in which venography has been routinely performed to classify venous outflow patterns.

Venous drainage was asymmetric in 9 (39%) of the 23 patients in this series. This finding suggests that asymmetric venous drainage from the cavernous and inferior petrosal sinuses may be much more common than previously thought. Six of the 9 patients had right side-dominant drainage despite patency of both left and right cavernous and inferior petrosal sinuses. The reason for this right side dominance is not clear, although similar patterns of preferential unilateral venous drainage, usually on the right, are well recognized variants in other venous sinuses of the brain (25). As evidenced by the remaining three patients, other patterns of asymmetric drainage can also occur, often as a result of an occluded segment of one of these sinuses.

TABLE 2. Two × two contingency table demonstrating the relationship between the venous drainage pattern and the ability of venous sampling to correctly lateralize tumor location

Lateralization	Venous drainage pattern			
	Cavernous sinus		Inferior petrosal sinus	
	Symmetric	Asymmetric	Symmetric	Asymmetric
Correct	12	3	12	4
Incorrect	2	4	2	5

Cavernous sinus sampling could not be performed in two cases due to occlusion at the mid- or high portion of the inferior petrosal sinus. Symmetric drainage patterns were associated with correct lateralization of tumor in 86% of cases, whereas asymmetric drainage was associated with correct drainage in only 44% of cases.

It is theoretically possible that the mass effect of an adenoma adjacent to the cavernous sinus could compress that sinus, causing a change in the normal venous outflow pattern and subsequent alteration in venous sampling data. Certainly, the possibility seems plausible in cases with large microadenomas or macroadenomas or tumors with extension into the cavernous sinus. Patient 14 in this series is one such example, in whom the microadenoma was located entirely in the left cavernous sinus and venography demonstrated an occluded left cavernous sinus. Although these situations are probably rare, the possibility that tumor size or location can alter venous outflow patterns should be considered where asymmetric drainage patterns are observed.

All tumors in this series were microadenomas that were not visible on MR imaging. The largest one identified at surgery was 6 mm in size, and excluding patient 14, it is, therefore, unlikely to have had a significant effect on outflow patterns. In fact, it is our policy not to perform venous angiography in any patient with Cushing's syndrome and a visible adenoma more than 4 mm in size on MR imaging, but to proceed directly with transsphenoidal exploration because the likelihood of this being an incidental finding is quite small. Nonetheless, this potential source of venous outflow destruction should be considered when a large adenoma is identified by MR imaging.

When drainage is predominantly unilateral, venous blood from the contralateral cavernous sinus will mix significantly with blood from the inferior petrosal sinus and possibly the cavernous sinus on the side of dominant drainage. Our findings suggest that this mixing can significantly affect measured ACTH concentrations in the venous sinuses, which, in turn, can affect the lateralization data obtained from bilateral sampling. We further hypothesize that the location of the adenoma in the pituitary gland will directly influence the magnitude and laterality of the gradient, such that venous drainage patterns must be considered when interpreting the lateralization data. For example, if a tumor is located ipsilateral to the side of dominant drainage, as in patients 11 and 18, the ACTH concentration on that side should be lower, as a result of dilution of ACTH concentration by venous blood from the contralateral side, than if drainage were symmetric. In contrast, if a tumor is located contralateral to the side of dominant drainage, as in patients 16 and 19, lateralizing gradients measured at the cavernous sinus might be relatively reliable, but gradients measured at the inferior petrosal sinus will probably be unreliable and discordant with the

cavernous sinus results. Shunting of ACTH-rich blood from the cavernous sinus on the side of the tumor into the contralateral inferior petrosal sinus would artificially elevate the ACTH concentrations on that side, whereas shunting of blood away from the opposite inferior petrosal sinus would reduce the ACTH concentration there, resulting in incorrect lateralization of the adenoma.

In the absence of corroborating data from other reports, we cannot draw firm conclusions about our findings in this study. Nonetheless, our results suggest that lateralizing gradients should be interpreted cautiously in patients with asymmetric venous drainage, especially if hemihypophysectomy is planned when no discrete tumor is found at surgery. In our series, hemihypophysectomy proved to be a correct surgical decision in seven patients with symmetric venous drainage, but was an incorrect decision in one patient with asymmetric drainage. More careful interpretation of the sampling data in light of this asymmetric drainage pattern may have prevented a hemihypophysectomy, leaving the patient with more treatment options, including adrenalectomy, medical therapy, or repeat sampling and surgical exploration at another time point.

Overall, venous sampling in the cavernous and inferior petrosal sinuses correctly lateralized the adenoma in 71% and 70% of patients, respectively. These accuracy rates are either better than or in close agreement with those of many other published series (1, 8, 10–18, 21, 25, 26). Because no other series has focused on the role of venous drainage in interpreting the results of venous sampling, we can only speculate about the relationship between asymmetric venous drainage and cases of incorrect lateralization reported in other series (21, 22, 26). However, it seems plausible that asymmetric venous drainage may account for a significant percentage of such cases.

Despite the observation that lateralization gradients were more accurate in cases of symmetric drainage than in cases of asymmetric drainage (86% vs. 42–44%), the difference showed a trend toward, but failed to achieve, statistical significance. This finding is most likely attributable to the relatively small sample size in each group and does not undermine the importance of the relationship between venous drainage and the reliability of lateralization gradients. Continued collection of these data will be required to confirm our suspicions in this regard.

Role of cavernous sinus sampling

Inferior petrosal sinus sampling is widely considered to be the best test for distinguishing Cushing's disease from other sources of ACTH-dependent hypercortisolism. However, in many cases, the ratio of inferior petrosal sinus to peripheral venous ACTH levels does not clearly differentiate these causes (1, 3, 8, 11, 25), although diagnostic accuracy can be improved by CRH stimulation (6, 10, 22, 26). In contrast, cavernous sinus sampling has a diagnostic accuracy of 100% in some series (21, 25, 27). In this series, cavernous sinus sampling confirmed a diagnosis of Cushing's disease in all 21 patients in whom it was employed (100%). The central to peripheral ACTH ratio in patients with Cushing's disease is higher with cavernous sinus sampling than with inferior

petrosal sinus sampling (25, 28), which increases the diagnostic accuracy of this test. Furthermore, the significantly higher ACTH levels with cavernous sinus sampling (25, 27) may largely obviate the need for CRH stimulation. In this series, ACTH levels were slightly higher in the cavernous sinuses than in the inferior petrosal sinuses, validating the conclusions drawn by others.

Inferior petrosal sinus sampling is less reliable at lateralizing the tumor than it is at establishing a diagnosis of Cushing's disease. Even CRH stimulation does not improve the accuracy of tumor localization (15, 22, 26). Cavernous sinus sampling is a potential improvement, because blood samples are obtained closer to the site of ACTH release into the perihypophyseal venous plexus. O'Neil *et al.* (27) recently reported a series of 30 patients in whom cavernous sinus sampling correctly lateralized the adenoma in 100% of cases, including 6 patients in whom previous pituitary surgery failed to identify a tumor. Teramoto *et al.* (25) also noticed that ACTH levels were generally much higher in the cavernous sinus than in the inferior petrosal sinus; however, cavernous sinus sampling correctly lateralized the tumor in only 75% of cases (25). In our series, tumors were localized equally well by cavernous sinus data and inferior petrosal sinus data. Our experience suggests that cavernous sinus sampling may yield slightly higher gradients than inferior petrosal sinus sampling; however, for purposes of lateralization, the primary limiting factor appears to be the venous drainage pattern rather than the sampling site.

Cavernous sinus sampling was nonlateralizing in cases in which inferior petrosal sinus sampling did lateralize. The central to peripheral ACTH ratio ipsilateral to the site of the tumor in two of these cases was less than 2:1, thereby failing to document Cushing's disease when inferior petrosal sampling did so. This finding suggests that in some situations, inferior petrosal sinus sampling may be more reliable than cavernous sinus sampling for diagnosing Cushing's disease and further supports the view that samples should be taken from both inferior petrosal and cavernous sinuses whenever possible to increase the diagnostic accuracy and reproducibility of venous sampling.

Cavernous sinus sampling is not routinely performed in many centers. It is technically more difficult than inferior petrosal sinus sampling (24, 25, 29) and carries a slightly higher theoretical risk for cranial nerve palsies and venous thrombosis (17). However, with the development of softer and finer catheters, this procedure has become safer, and we and others (21, 25, 27–29) have found no higher morbidity than with inferior petrosal sinus sampling alone (18). As venography requires catheterization of the cavernous sinus, and our data strongly support the need for venograms in every case, we now consider cavernous sinus sampling a standard part of the protocol for ACTH sampling in patients with clinical hypercortisolism.

Recommended approach to venous sampling in patients with Cushing's syndrome

We suggest that a gadolinium-enhanced MR image of the sella be obtained in all patients with ACTH-dependent hypercortisolism. If a discrete adenoma measuring greater than

4 mm is identified, further invasive sampling is probably not warranted, and a transsphenoidal resection is recommended. If MR images show no tumor or an adenoma less than 4 mm (potentially an incidental finding) (19, 25, 30), bilateral simultaneous cavernous sinus and inferior petrosal sinus sampling with or without CRH stimulation should be performed. A complete venogram of the basilar sinuses should be obtained before sampling to identify asymmetric drainage patterns that might affect interpretation of the lateralization data. Both inferior petrosal and cavernous sinus sampling should be performed when possible. When asymmetric venous drainage is identified, lateralization data should be interpreted with great caution, and a decision to perform a hemi- or total hypophysectomy should be appropriately weighted against all clinical evidence. When symmetric venous drainage is identified, much greater confidence can be placed in the accuracy of the lateralizing data, and hemihypophysectomy can be considered a safe option if no tumor is identified at surgery. Venography, therefore, appears to warn the surgeon against falsely lateralizing sampling data, which may, in turn, result in better surgical outcomes from hemihypophysectomy.

We anticipate that routine venography in patients with Cushing's disease will result in better and more accurate interpretation of lateralizing ACTH gradients and will lead to better surgical results in these difficult cases. Further experience with cavernous sinus sampling will be needed to define its full utility, but the need for venography in all patients undergoing inferior petrosal sinus sampling appears to be validated by these results, and we now consider it to be the standard component of the protocol for all patients undergoing venous sinus sampling of ACTH for suspected Cushing's disease.

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