AJNR

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AJNR Am J Neuroradiol 1996, 17 (9) 1669-1674
http://www.ajnr.org/content/17/9/1669

Bilateral Simultaneous Cavernous Sinus Sampling Using Corticotropin-Releasing Hormone in the Evaluation of Cushing Disease

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PURPOSE: To determine whether bilateral, simultaneous, cavernous sinus sampling after corticotropin-releasing hormone (CRH) stimulation offers as accurate detection and lateralization of Cushing disease as inferior petrosal sinus sampling does. **METHODS:** Seventeen consecutive patients with hypercortisolism and with high-dose dexamethasone suppression test results suggesting Cushing disease underwent bilateral cavernous sinus sampling with CRH stimulation. The diagnosis of Cushing disease was established in all patients by histologic examination or, if no tumor was found at surgery, by subtotal resection of the gland or radiation therapy resulting in eventual hypocortisolism or normal adrenal function and clinical remission. **RESULTS:** The sensitivity of cavernous sinus sampling with and without CRH in detecting Cushing disease was 94% and 71%, respectively. The abnormal side of the pituitary was correctly identified in all patients who had criteria for lateralization, yielding a positive predictive value of 100%. **CONCLUSIONS:** This small series suggests that cavernous sinus sampling with CRH is as accurate as inferior petrosal sinus sampling in detecting Cushing disease and perhaps more accurate in lateralizing the abnormality within the pituitary gland.

Index terms: Cushing disease; Cavernous sinus; Pituitary gland, hyperpituitarism; Interventional neuroradiology, provocative testing

AJNR Am J Neuroradiol 17:1669–1674, October 1996

Cushing syndrome is characterized by elevated levels of circulating corticosteroids. In the majority of cases (68%) it is caused by hypersecretion of corticotropin by the pituitary gland (Cushing disease). In 20% of cases it is caused by hypersecretion of cortisol by adrenal tumors that can be simulated by administration of exogenous steroids. In 12% of cases it is caused by hypersecretion of corticotropin by tumors outside the pituitary (ectopic corticotropin syndrome) (1, 2). Rarely, it can be caused by hypersecretion of corticotropin-releasing hormone (CRH) by the hypothalamus or by tumors outside the hypothalamus. Depression and alcoholism can also cause hypersecretion of CRH (3).

The high-dose dexamethasone suppression test is used to distinguish between hypersecretion of corticotropin by the pituitary and by an ectopic source. Patients with Cushing disease generally have greater than 50% suppression of urinary free cortisol and 17-hydroxysteroids with high-dose dexamethasone. In contrast, patients with ectopic corticotropin syndrome generally do not have greater than 50% suppression with high-dose dexamethasone; however, there may be considerable overlap in the values obtained with pituitary and ectopic sources of corticotropin hypersecretion (4).

Bilateral, simultaneous, inferior petrosal sinus sampling has been reported to have sensitivities and specificities of 95% and 100%, respectively, without CRH stimulation and 100% and 100%, respectively, after CRH stimulation in distinguishing between pituitary and ectopic sources of corticotropin hypersecretion (5);

Received July 5, 1995; accepted after revision March 5, 1996.

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AJNR 17:1669–1674, Oct 1996 0195-6108/96/1709–1669

Findings in 17 patients with hypercortisolism associated with Cushing disease

Patient	MR Finding	Met Baseline Cushing Criteria	Met Cushing Criteria after CRH Stimulation	Showed Lateralization before CRH Stimulation	Showed Lateralization after CRH Stimulation	Side of Lateralization	Side of Surgery	Surgical Finding	Pathologic Finding	Cure after Surgery	Long-term Result
1	L fullness	Yes	Yes	Yes	Yes	L	L	Tumor	Adenoma	No	Cure
2	R fullness	Yes	Yes	Yes	Yes	R	R	Tumor	Adenoma	Yes	Cure
3	Small gland	No	Yes	No	Yes	L	L	No tumor	Inconclusive	No	Cure
4	Normal	Yes	Yes	Yes	Yes	R	R	Tumor	Adenoma	No	Cure
5	L fullness	Yes	Yes	No	Yes	L	L	Tumor	Adenoma	No	Improved
6	L mass	Yes	Yes	Yes	Yes	L	. . .	Not feasible	. . .	. . .	Cure
7	R fullness	No	Yes	No	Yes	R	R	No tumor	Normal	No	Cure
8	R fullness	No	No	No	No	. . .	R	Tumor	Adenoma	Yes	Cure
9	Normal	Yes	Yes	No	Yes	L	L	Tumor	Adenoma	No	Lost to follow up
10	Normal	Yes	Yes	Yes	Yes	R	R	No tumor	Adenoma	Yes	Still in radiation therapy
11	Normal	Yes	Yes	Yes	Yes	R	R	Tumor	Adenoma	Yes	Cure
12	R fullness	Yes	Yes	Yes	Yes	R	R	Tumor	Adenoma	Yes	Cure
13	Normal	Yes	Yes	Yes	Yes	R	R	Tumor	Adenoma	No	No cure
14	Normal	Yes	Yes	Yes	Yes	R	R	Tumor	Adenoma	No	Still in radiation therapy
15	Normal	No	Yes	Yes	Yes	L	L	No tumor	Normal	Yes	Cure
16	Normal	No	Yes	No	Yes	R	R	Tumor	Adenoma	Yes	Cure
17	Normal	Yes	Yes	No	No	. . .	Midline	Tumor	Normal	Yes	Cure

Note.—CRH indicates corticotropin-releasing hormone.

however, inferior petrosal sinus sampling after CRH stimulation is able to determine the abnormal side of the pituitary in only 71% of cases (5).

The purpose of this investigation was to determine whether bilateral, simultaneous, cavernous sinus sampling after CRH stimulation offers as accurate detection and lateralization of Cushing disease as inferior petrosal sinus sampling does.

Materials and Methods

Clinical Information

We retrospectively reviewed the medical records of 17 consecutive patients who had a clinical diagnosis of hypercortisolism thought to be associated with Cushing disease and who underwent cavernous sinus sampling between 1988 and 1995 (see Table). All patients had a high-dose dexamethasone suppression test before cavernous sinus sampling.

Imaging Studies

Magnetic resonance (MR) imaging studies (at 1.5 T) were obtained in each patient before cavernous sinus sampling. Sagittal and coronal T1-weighted (500/14/1 [repetition time/echo time/excitations]) images were obtained before and after intravenous administration of gadopentetate dimeglumine through the pituitary gland with the use of contiguous 3-mm-thick sections. Axial T2-weighted (3000/30,100/.5 [rectangular field of view]) images were obtained through the brain. Findings on MR images were classified as normal, as showing an asymmetric fullness, or as showing a discrete mass.

Cavernous Sinus Sampling Procedure

Ovine CRH (Ferring Pharmaceuticals; Suffern, NY) was used under the manufacturer's investigational new drug exemption after approval was obtained from our institution's Investigational Review Board. Written consent was obtained for the cavernous sinus sampling and for the use of CRH.

After intravenous administration of a sedative and a local anesthetic, a 7F sheath was placed in both common femoral veins. Heparin (5000 U) was administered intravenously, with an additional 1000 U administered every hour during the procedure.

The 45°-angled tip of a 7F catheter tapered to a 5F catheter (Berenstein; Bard, USCI Division, Billerica, Mass) was positioned in the jugular bulb. A wire-guided 3F microcatheter tapered to a 2.7F microcatheter (Tracker Hi-Flow; Target Therapeutics, Fremont, Calif) was passed through the 7F catheter and inferior petrosal sinus into the cavernous sinus. The tip was positioned at the junction of

the cavernous sinus and the inferior petrosal sinus. Digital subtraction angiography of the cavernous sinus was performed to confirm the catheter's position. A second microcatheter was positioned in a similar manner on the opposite side.

Simultaneously, 2-mL samples of venous blood were obtained from both microcatheters and from a peripheral vein before, 5 minutes after, and 10 minutes after the intravenous injection of ovine CRH (1 μg/kg). Plasma was immediately prepared from the blood samples and kept frozen at −5°C until an assay was performed. Normal saline was infused continuously through the guiding catheter during the procedure. Normal saline was infused continuously through the microcatheter when blood was not being withdrawn.

Corticotropin Levels and Ratios

The venous corticotropin levels from both sides of the cavernous sinus and a peripheral vein were used to calculate side-to-side intercavernous sinus and bilateral cavernous sinus:peripheral vein ratios. Each of these ratios was calculated before, 5 minutes after, and 10 minutes after CRH administration. A maximum cavernous sinus:peripheral vein ratio of at least 3:1 was considered suggestive of Cushing disease (5). A maximum intercavernous sinus ratio of at least 1.4:1 was used to indicate lateralization of corticotropin levels (5, 6).

Surgery and Histopathology

Surgical findings were obtained from surgical reports. Data concerning pathologic findings were obtained from pathologic specimen reports. Histopathologic analysis included conventional hematoxylin-eosin staining as well as immunohistochemical staining for corticotropin, prolactin, and growth hormone (7).

Analysis

Similar to Oldfield et al (5), we considered the diagnosis of Cushing disease to be established when confirmed by histologic examination or, if no tumor was found at surgery, when subtotal resection of the gland or radiation therapy resulted in eventual hypocortisolism or normal adrenal function and clinical remission.

Again like Oldfield et al (5), we identified the abnormal side of the pituitary gland by surgical and histopathologic findings. We also established the abnormal side by findings of a discrete pituitary mass on MR images or when resection of that side resulted in a clinical remission.

Results

Clinical Information

The study group included 10 female and seven male subjects with a mean age of 31 years (range, 9 to 60 years; SD, 36). All patients had high-dose dexamethasone suppression test results that were suggestive of Cushing disease (2, 8).

One patient (case 3) had previously undergone successful transphenoidal surgery for Cushing disease and had been disease free for 5 years. He was referred to our institution because of recurrent disease.

One patient (case 1) had had a bilateral adrenalectomy as a palliative measure 4 years previously. She had never had pituitary surgery. Her referral was prompted by the development of Nelson syndrome.

All 17 patients had surgery for Cushing disease. Seven of the patients (cases 2, 8, 11, 12, and 15 through 17), including two who had normal histopathologic findings (case 15 and 17), are now free of disease after surgery alone. One patient (case 10) was initially cured after surgery, but had a recurrence 4 years later and was referred to us for radiation therapy.

Of the eight patients who were not cured after surgery, seven have had further therapy. Six are now free of disease and one is significantly improved: four received radiation therapy (cases 1, 4, 7, and 10); one received radiation therapy and adrenalectomy (case 6, for whom surgery was not possible); one received adrenalectomy alone (case 3, in whom surgery was unsuccessful); and one underwent a second pituitary surgery (case 5). The remaining patient (case 13) will undergo a second pituitary surgery in the future.

The pituitary mass of one patient (case 6) could not be resected because of intraoperative bleeding. This patient underwent radiation therapy and adrenalectomy and is now free of disease.

Imaging

Findings on MR images of the pituitary region were normal in 10 patients. In one of these (case 3), who had previous pituitary surgery, a small pituitary gland was noted. In the remaining seven patients (cases 1, 2, 5 through 8, and 12) the MR findings were abnormal. Six of these studies showed asymmetric fullness of the gland (9, 10) and one (case 6) showed a discrete residual or recurrent nonenhancing mass measuring 3 mm on one side of the gland.

Cavernous Sinus Sampling

It was possible to catheterize and obtain samples from both sides of the cavernous sinus in all patients. No complications were encountered.

Corticotropin Levels and Ratios

Twelve patients (71%) had a baseline cavernous sinus:peripheral vein ratio of at least 3:1 (mean, 23.9; SD, 29.1; ratio range, 3.1 to 109.4). Five patients had a baseline cavernous sinus:peripheral vein ratio less than 3:1 (mean, 1.3; SD, 0.6; ratio range, 1.0 to 2.3).

Sixteen patients (94%) had a cavernous sinus:peripheral vein ratio of at least 3:1 (mean, 295.5; SD, 914.9; ratio range, 3.3 to 3714.3) after CRH stimulation. The remaining patient (case 8) had a cavernous sinus:peripheral vein ratio of 1.3 with a baseline ratio of 1.0.

Of the 12 patients with a baseline cavernous sinus:peripheral vein ratio of at least 3:1, 10 (83%) had an intercavernous sinus ratio of at least 1.4:1 (mean, 11.5; SD, 6.5; range, 2.4 to 24.5) and thus met the criteria for lateralization. Of the 16 patients with a cavernous sinus:peripheral vein ratio of at least 3:1 after CRH stimulation, 15 (94%) had an intercavernous sinus ratio of at least 1.4:1 (mean, 34.3; SD, 90.1; range, 1.8 to 351.8).

None of the 10 patients who had a baseline intercavernous sinus ratio of at least 1.4:1 had reversal of the ratio after CRH administration.

One patient (case 15) had a baseline cavernous sinus:peripheral vein ratio of 1.7 and an intercavernous sinus ratio of 1.7. After CRH stimulation, this patient had a cavernous sinus:peripheral vein ratio of 8.7 and an intercavernous sinus ratio of 3.4.

Surgery and Histopathology

Sixteen of the patients had subtotal resection of the pituitary gland via a transphenoidal approach. At surgery, seven patients were thought to have a microadenoma (cases 2, 4, 5, 8, 13, 14, and 16), five a diffuse tumor (cases 1, 9, 11, 12, and 17), and four a normal gland (cases 3, 7, 10, and 15). The pituitary mass of one patient (case 6) could not be resected because of intraoperative bleeding.

Histopathologic examination revealed an adenoma in 12 (75%) of the patients. This included 11 of the 12 patients (cases 1, 2, 4, 5, 8 through 14, and 16) who were found to have a microadenoma or diffuse tumor at surgery and one (case 10) who had no abnormality noted at surgery. No histopathologic finding of tumor was noted in the other two patients (cases 7 and 15) who had no abnormality at surgery. Histopathologic findings were inconclusive in the remaining patient (case 3) who had no abnormality at surgery. This patient had undergone surgery 5 years prior to the cavernous sinus sampling and repeat surgery.

One patient (case 8), who had a cavernous sinus:peripheral vein ratio of 1.0 before and after CRH stimulation, went on to surgery because of a strong clinical suspicion of Cushing disease and an MR study that showed fullness in one side of the gland. At surgery, a small tumor was resected. Histopathologic examination revealed a pituitary adenoma that was positive for corticotropin by immunohistochemical staining.

Analysis

The diagnosis of Cushing disease was made in 17 of our patients on the basis of the criteria described above: histopathologic examination of the transphenoidal surgical specimen revealed an adenoma in 12 patients; three patients (cases 3, 15, and 17) with normal histopathologic findings had a clinical remission after transphenoidal surgery; and two patients (cases 6 and 7) had a clinical remission after radiation therapy.

Of the 17 patients with the diagnosis of Cushing disease, 12 met the baseline cavernous sinus:peripheral vein ratio criteria and 16 met the post-CRH stimulation cavernous sinus:peripheral vein ratio criteria for Cushing disease. These results indicate baseline and post-CRH stimulation cavernous sinus:peripheral vein sensitivities of 71% and 94%, respectively, for detecting Cushing disease.

Of the 16 patients with the diagnosis of Cushing disease in whom surgery was successful, nine showed lateralization before CRH stimulation and 14 showed it afterward. All of these correctly lateralized to the abnormal side of the gland, which indicates a positive predictive value of 100% for the baseline and post-CRH stimulation intercavernous sinus ratios.

In one patient (case 8) who had normal cavernous sinus:peripheral vein ratios, there was no lateralization. In one patient (case 17) with

cavernous sinus:peripheral vein ratios indicative of Cushing disease and a midline tumor at surgery, there was no lateralization.

Discussion

Inferior petrosal sinus sampling is considered by many to be the standard of reference for distinguishing between pituitary (Cushing disease) and ectopic (ectopic corticotropin syndrome) causes of corticotropin hypersecretion (1, 5, 6, 11–23). This assumption is based on the premise that hypersecretion of corticotropin by tissue in the sella will result in elevated levels of corticotropin in venous effluents of the pituitary gland, including the inferior petrosal sinus. The addition of CRH sampling is thought to assist further in differentiating between pituitary and ectopic causes of corticotropin hypersecretion because only pituitary causes are responsive to CRH stimulation (5).

Bilateral, simultaneous, inferior petrosal sinus sampling has been reported to have sensitivities and specificities of 95% and 100%, respectively, without CRH stimulation and 100% and 100%, respectively, after CRH stimulation in distinguishing between pituitary and ectopic sources of corticotropin hypersecretion (5).

For our small group of patients, cavernous sinus sampling, with and without CRH stimulation, was able to show Cushing disease in 94% and 71%, respectively, of our patients (ie, sensitivities). We had no true-negative results (ie, patients with an ectopic source of corticotropin and a negative cavernous sinus:peripheral vein ratio); therefore, specificities could not be calculated.

In patients with Cushing disease, inferior petrosal sinus sampling after CRH stimulation is able to determine the abnormal side of the pituitary gland in only 71% of cases (5). In each of our patients with Cushing disease with lateralization, the abnormal side of the gland was correctly identified with or without CRH stimulation (positive predictive value, 100%). Oldfield et al (6) used only surgery and histopathologic examination to determine the abnormal side of the pituitary gland. With the use of surgery and histopathologic examination alone, the positive predictive value of cavernous sinus sampling after CRH stimulation to determine lateralization in our patients with Cushing disease was 94%. Fifteen of 16 patients who had surgery had intercavernous sinus ratios that were congruent with surgical findings.

MR imaging is invaluable in the examination of the pituitary gland and parasellar region. Pituitary adenomas often can be detected by MR imaging; however, this technique can be somewhat limited in patients with Cushing disease. The adenomas responsible for this disease are often quite small, making them the most difficult microadenomas to detect (9, 10). These adenomas attract clinical attention because of their metabolic rather than their mass effect. In only about 40% of our patients did preoperative MR imaging reveal an abnormal contour to the pituitary gland. A definite mass lesion was seen in only one patient. Therefore, another means of determining the abnormal side of the pituitary was necessary before surgery.

The results of initial surgical therapy in our group of patients are somewhat disappointing. Only eight patients with Cushing disease had a complete long-term cure from surgery alone. Radiation therapy, adrenalectomy, or additional pituitary surgery was necessary in the other patients to obtain significant clinical improvement or remission.

Technical and anatomic factors that can complicate inferior petrosal sinus sampling have been described (1). These same factors apply to cavernous sinus sampling. In addition, with cavernous sinus sampling there is the potential to catheterize a more proximal dural venous sinus. Possible complications of cavernous sinus sampling include those related to any vascular catheterization. Neurologic complications of inferior petrosal sinus sampling have been reported. Brain stem injury occurred in 0.2% of patients undergoing inferior petrosal sinus sampling in the largest series reported to date (24). The potential for brain stem injury as well as for cavernous sinus thrombosis exists during cavernous sinus sampling. No complications, neurologic or otherwise, were observed in our patients.

In conclusion, bilateral cavernous sinus sampling is potentially more costly, time consuming, and dangerous than inferior petrosal sinus sampling because of the need to pass microcatheters through the inferior petrosal sinus into the cavernous sinus bilaterally. However, we believe that the potential benefits of more accurate lateralization are greater than the potential disadvantages of cavernous sinus sampling. More information is required before final com-

parisons can be made between inferior petrosal sinus and cavernous sinus sampling techniques in patients with Cushing syndrome.

Acknowledgment

We thank Jacqueline Chazaly for assistance in assembling the case material.

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