AJNR

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AJNR Am J Neuroradiol 1998, 19 (7) 1245-1246
http://www.ajnr.org/content/19/7/1245.citation

LETTER

Evaluation of Cushing Disease: Cavernous or Inferior Petrosal Sinus Sampling?

I read with great interest the article by Oliverio et al, "Bilateral Simultaneous Cavernous Sinus Sampling Using Corticotropin-Releasing Hormone in the Evaluation of Cushing Disease" (1) and would like to discuss some general problems regarding both cavernous sinus sampling and inferior petrosal sinus sampling.

First, I agree with Oliverio et al (1) that "bilateral cavernous sinus sampling is potentially more costly, time consuming and dangerous than inferior petrosal sinus sampling." Conversely, I'm not sure that the catheterization of the cavernous sinuses through microcatheters can always improve the predictive value of sampling in lateralizing pituitary lesions.

In fact, Doppman et al (2) stated that no further information about gradient levels or lateralization can be obtained from "superselective" cavernous sinus sampling. These investigators also reported that hormonal concentrations in the inferior petrosal sinus should not increase above the origin of the basilar plexus (3). I perform venous sampling using four or five French catheters with no side holes and 45°-angled tip. I consider the catheter tip in the correct position when it lies in the passage between the vertical and horizontal segments of the inferior petrosal sinus, and above the origin of the anterior condylar vein, vertebral venous plexus and basilar plexus. If it is impossible to position the catheter correctly, I leave the tip lower down, beneath the origin of these vessels (4).

On the other hand, Oliverio et al (1) didn't catheterize the cavernous sinus precisely, but positioned the catheter tip at the junction of the cavernous sinus and the inferior petrosal sinus. Are the hormonal concentrations at this level different from the concentrations at the junction of the vertical and horizontal segments of the inferior petrosal sinus?

Inferior petrosal sinus sampling is also open to criticism. I know that in some cases the inferior petrosal sinus doesn't represent the main draining vein from the cavernous sinus (4): In these cases inferior petrosal sinus sampling may imply false negative results and cavernous sinus sampling might be more efficacious. Unfortunately, inferior petrosal sinus venography is not able to establish exactly the main venous drainage from the cavernous sinus. In fact, there is a forced retrograde opacification of the veins during inferior petrosal sinus phlebography. I believe that only the venous phase of bilateral carotid arteriography can show the venous drainage from the cavernous sinus (4).

I believe that using microcatheters—like Oliverio et al (1)—makes it difficult to perform perfectly timed samples because of the limited rate of aspiration, compared to 5 (or 4) French catheters.

I should also point out that, in their paper, Oliverio et al (1) didn't specify why venous sampling was performed on patients with abnormal MR findings and high-dose dexamethasone suppression tests suggestive of Cushing disease. Were the suppression test results by any chance doubtful rather than suggestive of Cushing disease? Otherwise, in cases of abnormal pituitary MR findings and suppression test results suggestive of Cushing disease, is it justified to perform venous sampling to exclude pituitary "incidentaloma"?

Doppman et al reported that venous sampling should be performed on patients "with ACTH-dependent hypercortisolemia and a normal MR of the pituitary gland" and on patients "with ACTH-dependent hypercortisolemia, an abnormal pituitary MR, but with equivocal suppression and stimulation test (2)."

I emphasize the need to establish definitively how and when to carry out venous sampling in Cushing syndrome, because this procedure is invasive and potentially dangerous. Moreover, keeping in mind the increasing pressure for cost-containment in healthcare, venous sampling (cavernous sinus sampling more than inferior petrosal sinus sampling) is of questionable efficacy if performed on unselected patients.

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Reply

We appreciate the opportunity to respond to the comments of Calzolari. There is little information in the literature comparing the advantages and disadvantages of inferior petrosal and cavernous sinus sampling in patient's with Cushing disease (1–3). Because it would be difficult to simultaneously sample the inferior petrosal and cavernous sinus after a single dose of corticoptropin releasing hormone (CRH), there are no published data comparing simultaneous inferior petrosal and cavernous sinus sampling after CRH stimulation. There is little published literature concerning cavernous sinus sampling after CRH stimulation.

Doppman found cavernous sinus sampling without CRH stimulation to be less useful in lateralizing adenomas than inferior petrosal sinus sampling with CRH stimulation (2). In contrast, Alazzaz (1) and Mamelak (3) found that cavernous sinus sampling without CRH stimulation was more useful than inferior petrosal sinus sampling without CRH stimulation. Since we only sampled the cavernous sinus after CRH stimulation, our data must be compared to the published data regarding inferior petrosal sinus sampling. In patients with Cushing disease, Oldfield et al (5) reported that inferior petrosal sinus sampling after CRH stimulation can determine the abnormal side of the gland in only 71% of cases. In each of our cases of Cushing disease with lateralization, the abnormal side of the gland was identified using cavernous sinus sampling with or without CRH stimulation (positive predictive value, 100%). We therefore, believe, in contrast to Dr. Doppman and Calzolari, that the "jury is still out" on which of these techniques is better able to determine lateralization of adenomas.

When comparing the relative ease of withdrawing blood samples from four or five French catheters used for inferior petrosal sinus sampling versus the microcatheters we use for cavernous sinus sampling, we had no difficulty withdrawing adequate samples in a timely fashion by using microcatheters.

We agree with Dr. Calzolari and Doppman that inferior petrosal sinus sampling is most useful in patients with "ACTH-

dependent hypercortisolemia and a normal MR [without an obvious adenoma] of the pituitary gland" and in patients "with ACTH-dependent hypercortisolemia, an abnormal pituitary, but with equivocal suppression and stimulation test." Ten of our patients met the former criteria with totally normal MR scans. Six additional patients met the former criteria with "fullness" but no discrete abnormality. One patient (case 6) had previous surgery with a recurrent or residual adenoma and persistent Cushing disease. Further confirmation of the side of the gland with hypersecretion was warranted before reoperation. None of our patients met the latter criteria.

We agree with Dr. Calzolari that this procedure be reserved only for patients whom have been shown to have Cushing disease by high dose dexamethazone suppression test and who are felt to have Cushing disease by an endocrinologist. If these criteria are adhered to, the procedure will be utilized in an appropriate and judicious manner. Furthermore, the costs and risks of the procedure are acceptable to provide accurate presurgical lateralization of tumor given the risks and costs associated with inaccuracy in this situation.

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