MAR Neurology

Research Article

Cushing Disease with Negative Sellar MRI: The Value of Inferior Petrosal Sinus Sampling

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Abstract

Cushing's disease is a neuroendocrine disorder associated with multiple potentially devastating side effects related to cortisol hypersecretion. Pituitary tumors of Cushing's disease are usually microadenomas, whose diameter is by definition equal to or less than 10 mm. These tumors are most often discovered when the clinical manifestations of hypercortisolism resulting from ACTH hypersecretion. In a minority of patients an IPSS -the most sensitive method for differentiating between pituitary and ectopic- ACTH secretion may be a useful tool for locating some unobserved pituitary micro-adenomas on MRI. The authors present eight patients with Cushing syndrome and negative sellar MRI, operated by transsphenoidal technique. All patients underwent IPSS to confirm a central to peripheral ACTH gradient and to localize the side of excess ACTH production in the pituitary gland. In 05 of 08 patients, the lateralization was correct with tumor found on the predicted side during surgery. in two patients, no tumor was found during surgery but diffuse clusters of corticotropic pituitary adenoma cells were found on histological examination of the resected portion of the gland. All patients underwent a transsphenoidal approach. In six patients, selective excision of the tumor with sparing of the normal pituitary gland was achieved. Two adult men underwent a Hemi hypophysectomy oriented by IPSS. Our study outlines that IPSS is useful in establishing a pituitary source for Cushing's disease. IPSS is considered to be the gold standard for confirming the origin of ACTH secretion in patients with Cushing's syndrome, or those who needed pituitary surgery.

***Keywords**: Cushing disease, IPSS, hypophysectomy, brain MRI.*

Abbreviations used in this work

ACTH = adrenocorticotropic hormone;

CD = Cushing's disease;

CRH = corticotropin-releasing hormone;

EAS = ectopic ACTH secretion;

IPSS = inferior petrosal sinus sampling;

MRI = magnetic resonance imaging.

Introduction

CD or pituitary-dependent Cushing's syndrome is the most common form of endogenous CS, accounting for around 70% of the forms of chronic endogenous hypercortisolism.

In the case of hypercortisolemia results from an ACTH–dependent process, approximately 80% are due to a pituitary adenoma (Cushing's disease [CD]), 10% are due to adrenal lesions, and 10% are secondary to ectopic ACTH secretion.

Recent pituitary MRI techniques, like dynamic sequences, improved the tumor detection rate. When a pituitary tumor is not convincingly identified, IPSS remains the gold standard for diagnosis, and recently, new approaches (simultaneous prolactin measurement) could improve its sensitivity and specificity. In 40 to 50% of cases with Cushing disease and biochemical hypercortisolemia have no visible adenoma on MRI. **(**1,2**)**

The purpose of this study was to evaluate the correlation between the intraoperative visualization of the tumor and surgical remission with IPSS results.

Materials and methods

We analyzed 08 patients with ACTH–dependent Cushing syndrome. The patients presented in this article concerned 06 young adults and 02 children, the mean age was 31,5 years, sex ratio 6W/2M, Central obesity and skin thinning with purplish striae, and diffuse bruising were the most frequent symptoms of this disease, followed by high blood pressure.

Sellar MRI was performed in all our patients, the adenoma was not visualized in 100% of the cases

-IPSS: all patients underwent IPSS to confirm a central to peripheral ACTH gradient and to localize the side of excess ACTH production in the pituitary gland.

The transsphenoidal approach was used in all patients. After opening the sellar floor and sellar dura, the pituitary gland was exposed. After identification, a selective adenectomy was performed.

When no adenoma was seen, the gland is entirely explored. If no tumor was found, a part of the gland was excised. The tissue was sent for pathological examination. In our study, no histological examinations were performed intraoperatively. Pituitary specimens were analyzed by the same pathologist and the presence of ACTH-secreting cells was evaluated by immunocytochemistry using specific anti-ACTH antibodies.

Antisera were directed against pituitary hormones, growth hormone, prolactin, ACTH, follicle-stimulating hormone, luteinizing hormone, and thyrotropin; both MIB1 and p53 labeling indices were evaluated. In all patients, serum cortisol was assayed three or four days after surgery before the replacement hydrocortisone was administered.

When they remained clinically well and free of complications (03 days after surgery), patients were oriented then followed up in our endocrine clinic or by the referring endocrinologists.

The patients were considered to be in remission when: *their cortisol levels (serum cortisol) remained within normal limits or low range requiring replacement hydrocortisone therapy.*

- *they required ongoing replacement hydrocortisone therapy.*
- *they were clinically free of signs and symptoms of Cushing's disease. The mean follows up in this series was 20 months (range 6 - 50 months).*

Results

There was no procedure-related (IPSS) severe morbidity. No major perioperative complications, including hypopituitarism, occurred in this series.

The CD confirmed in all patients by histological examination (100 % sensibility of IPSS) In 06 cases a localized tumor was found during exploration, In 05 of 08 patients, A gradient greater than 1.4 across both sides of the pituitary found the lateralization was correct with the tumor found on the predicted

side during surgery (3 right, 2 left). (correct lateralization in 62,5 %). In 02 cases the gradient was inferior to 1 and equal to 1.3 in one case.

In two adult men, no tumor is found after exploration, removal of the half of the gland oriented by IPSS was realized (Hemi-hypophysectomy), after histological examination, clusters of corticotropin-staring pituitary adenoma cells are found, indicating diffuse involvement of the pituitary gland.

From 06 patients who had serum cortisol in the normal range,02 patients have a recurrence during the follow-up and from 02 patients who had undetectable basal serum cortisol, no recurrence was noted.

Discussion

According to the recommendations of the American Endocrine Society, co-signed by the European Society of Endocrinology, the diagnostic strategy for ACTH-dependent hypercorticism is as follow: in the event of a positive response to both dynamic tests (CRH and strong braking) and of the pituitary image at MRI> 6 mm, the diagnosis of CD is confirmed. In all other cases (discordant, negative tests, absence of clear pituitary image) and the absence of neoplasia evident on thoracic-abdominopelvic CT scan, catheterization of the petrous sinuses should be considered.

IPSS is a highly sensitive and specific examination series reporting near 100% values for both. Exact ratio values will vary between institutions. Typically published ratios are:

In CD, a central-to-peripheral ACTH gradient is found and its contrast with the absence of a gradient in EAS secretion. Without CRH administration, a basal ratio of central/peripheral ACTH values of 1.7 or greater is strongly indicative of CD.

CRH is used to increase the sensitivity of the test. Plasma ACTH samples are obtained from inferior petrosal sinuses and peripherally after CRH administration. A central/peripheral ACTH ratio of 3.3 or greater is strongly indicative of Cushing's disease. Most patients with EAS have a central/peripheral ACTH ratio of less than 1.8.

In our series sensibility of IPSS was 100 %, the CD confirmed in all patients by histological examination, similar to Oldfield et al3 results, IPSS seems to have values close to 95% **(**4,5**)**

In our series, we have correct lateralization in 62.5% close to the results of Wind10, A literature review, in which the authors analyzed data from 313 cases in which lateralization studies had been performed and used pituitary surgery as the criterion, revealed a range of diagnostic accuracy for localization of IPSS between 50 and 100%. **(**6**)**

A gradient of 1.4 or greater across both sides of the pituitary correctly predicted tumor location in 78% of cases. **(**7,8**)**

The prediction of lateralization of the adenoma is 57 to 80% depending on the studies if one of the sides has ACTH levels greater than 1.4 times those of the contralateral side (the highest sinus values indicating the side where the surgeon is most likely to find the adenoma). When the veins are of similar diameters and the catheterization symmetrical, the localizing value seems higher **(**5,9**)**. In these series, Wind found an inter petrous ratio at 1.4 in 98% of the cases, with correct lateralization in only 69% **(**10**)**. The catheterization of the petrous sinuses should therefore not be used to locate the adenoma.

Complications of IPSS (venous thrombosis, stroke, paralysis of the cranial nerves, arteriovenous fistulae) are rare (inferior to 0.2%) **(**4,9,11**)**. It's still an expensive and invasive diagnostic approach, which must be performed by an experienced interventional radiologist in centers with great expertise and experience performing the procedure and only if indicated when patients have confirmed ACTH dependent CS. ACTH secreting pituitary microadenomas, which may be inapparent on imaging in 40 to 50% of cases, account for 80% of non-adrenal, non-iatrogenic cases.

When the adenoma is not visible when the dura mater is opened, the entire gland must be explored with parallel incisions. If, after this, no tumor is identified, the inferior mesial portion of the gland is then dissected through a transverse incision, leaving a central wedge of the gland still attached to the pituitary stalk. The operation is typically considered complete at this stage in pediatric patients and women of childbearing age who desire fertility. In other patients, the decision to undertake hypophysectomy is made on a case-by-case basis, depending on the patient's condition and prior operations and results of laboratory studies and inferior petrosal sinus sampling. **(**14**)**

If the adenoma is not found after exploration, it is recommended to perform a Hemi hypophysectomy based on the inter sinus gradient found during catheterization of the lower petrous sinuses, if it is greater than or equal to 1.4 (knowing that it has a very average locating value as we have seen previously).

A meticulous exploration of the sella, by an expert surgeon, allows the identification of a microadenoma in 85 to 90% of cases **(**12**)**. In the series of Sun et al, In 2012, comprising 119 patients including 24 with MRI negative, pituitary adenoma was found in 83.3% of cases when imaging was negative compared to 93.6%when it was positive **(**13**)**.

Conclusion

Our study outlines the importance of long-term follow-up in patients with Cushing's disease with a normal MRI of the pituitary area. The success of the surgery and the outcome of these patients depends first on a large communication between all members of the management team, the second: a degree on the experience and expertise of the management team as well as the location, extent, and the invasive nature of the adenoma.

Our study outlines that IPSS is useful in establishing a pituitary source for Cushing's disease. IPSS is considered to be the gold standard for confirming the origin of ACTH secretion in patients with Cushing's syndrome, patients who needed pituitary surgery.

Conflicts of interest: *The authors report no conflicts of interest.*

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