

## A Surgical Remission in the Cushing Disease with Normal MRI of the Pituitary Area

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### Abstract

**Introduction:** Microadenomas are usually responsible of Cushing's disease resulting from hypersecretion of ACTH. In a significant minority of patients with Cushing disease who a microadenomas are not found during imaging performed for this reasons, a IPSS can be a useful tool in localizing some pituitary micro adenomas no definitively observed on MRI.

**Material and Method:** Twelve [12] patients have normal MRI of the pituitary area. The average age of the patients was 24 years. Sex ratio was 05 females versus 07 males.

Preoperative imaging:

- all our patients benefit from MRI, the adenoma was not visualized in 100% of the cases

-IPSS: 12 patients underwent IPSS to confirm a central to peripheral ACTH gradient and to localise the side of excess ACTH production in the pituitary gland.

All patients underwent direct Microsurgical endonasal transsphenoidal approach with the patient in a semi-sitting position during surgery.

7 of our patients have benefited of selective excision of the microadenoma. Three (03) patients underwent a hemi hypophysectomy oriented by IPSS.

**Conclusion:** It is very important to follow the patients in consultation for a long time in order to detect a progressive resumption of the disease

**Keywords:** Cushing Diseases; IPSS; Hypophysectomy; Cerebelar MRI

### Introduction

the pituitary origin of cushing's disease remains difficult to confirm, especially if there is no microadenoma on brain MRI mais la realisation de l'IRM hypophysaires en séquences dynamiques, a amélioré le taux de détection des microadenomes. The influence of

preoperative pituitary MRI findings on surgical outcome is also controversial, however the pituitary MRI remains the first radiological examination to be requested of the sella to detect a focal pituitary gland lesion and remains an important component of the pre-therapeutic work up. if there is no lesion in the pituitary gland after dynamic cerebral MRI, taking samples from the inferior petrosal sinus (IPSS) can be a useful tool to confirm the pituitary origin of the ACTH secretion.

The aim of our presentation of this study is to show the interest of taking samples from the inferior petrosal sinus in the presence of cushins disease without adenomas visible on brain MRI.

Patients and methods: study protocol

Between January 2004 and October 2019, 65 patients with CD underwent direct Microsurgical endonasal transsphenoidal at Bab el Oued, and Tizi ouzou Hospital. The data of 12 patients who had negative pituitary MRI out of the 65 patients with cushing’s disease were retrospectively analyzed.

of the 12 patients,10 were young children and 2 were small children (Table 1). for the follow-up of our patients we had an average follow-up of 3.8 years.

	Number of patients	Percentage
F	5	41,6
H	7	58,3
Total	12	100,0

Table 1

Age varies between 11years and 45years.

All these patients underwent microsurgical endonasal transsphenoidal route.

Our operative tumor specimens benefited from an anatomo-payhological study and also included an immunocytochemical analysis in all patients.

A postoperative hormonal assessment was performed in all our patients on the third day. On the fourth postoperative day, our patients are returned to the endocrinology department for clinical and biological follow-up and evaluation.

To assess remission in our patients we used the following clinical and biological criteria

- A postoperative cortisol level (serum cortisol) which remains within normal limits or within a low range requiring hydrocortisone replacement therapy.
- A good clinical state (stabilization of the hemodynamic state and regression of some symptoms of Cushing’s disease).

Results

Remission was obtained in 07 (63.63%) of the 12 patients who had a positive inferior petrous sinus sample (IPSS).

During the follow-up of our patients, we found three cases of recurrence of the disease.

We don't have any major perioperative incident or complications, but in the immediate postoperative period one of our patients presented with severe hemodynamic disorders leading to the death of the patient despite adequate reanimation.

The clinical signs most frequently found in our patients are represented by obesity and multiple stretching of large varicose veins in the abdomen, associated with high blood pressure.

Two patients had clinically severe disease (psychiatric and cardiac disorders).

In all of our 12 patients, the adenoma was not visualized in 100% of cases on pituitary MRI, these 12 patients underwent IPSS, In 08 of the 12 patients, the IPSS examination showed a lateralization of the secretion of ACTH. while in three 03 patients, he just confirmed the central origin of the secretion and effectively during per operative surgery no lesion or adenoma was found.

### Operative technique

The microsurgical endonasal technique was used in all patients. once the sellar dura is opened, the pituitary gland is explored superficially, once the adenoma has been identified, a selective adenomectomy associated in some cases with the ablation of the healthy peripheral tissue has been performed In 09 of these 12 patients and when no adenoma after intra glandular surgical exploration has been found, I proceed to the realization of a hemihypophysectomy in three (03) patients

Of the 12 patients with a normal MRI 08 patients had a microadenoma found and removed oriented by IPSS and in one case a microadenoma was found while the IPSS did not show any lateralisation it did not guide us. In three cases, there was no identified tumor.

### Histological examination

In our series, no histological examinations were performed intra operatively; all were realized post operatively. All our anatomopathological and immunohistochemical analyzes were carried out postoperatively by the laboratory of our hospital. In three patients, a normal pituitary gland was found Histological confirmation was obtained in only 72.72% of patients with normal MRI.

### Out come

Three patients developed recurrence of high level cortisol : they accepted sub sequent operation, irradiation.

In our series the criteria that we have retained to say whether our patients are in remission or not, are the regression of clinical signs and the normalization at least of the postoperative hormonal status.

Serum cortisol was measured in 11 patients three days after surgery:

In 07 patients (63,63%) the serum cortisol was in the normal range.

In 04 patients (36,36%) the serum undetectable basal serum cortisol.

The duration of recurrence in our series is variable, for example in the 7 patients who had a cortisol level within the limit of normal in postoperatively with an acceptable clinical state (disappearance of certain clinical signs) 2 patients have biologically recurrence (hypercorticism) within 03 years, whereas for the 04 patients who had collapsed postoperative cortisol levels, only one patient recurred clinically (reappearance of symptoms) and biologically (hyper corticosteroid) in 04 years

### Discussion

The efficacy of the MR imaging in localizing a microadenoma in the sellar area has been stressed. de Herder [13], Invitti, *et al.* [19] studied 288 patients with CD and encountered an adenoma in the location corresponding to the MR imaging in 87% of them, whereas the IPSS accurately lateralized the adenoma in 68% of patients. De Herder, *et al.* [13] have demonstrated a correct localization of the tumor in 93% of 15 patients with a positive MR imaging study, whereas the IPSS localized the correct side in 73%. Our results are similar; the IPSS correlated with the location of the adenoma in 70%. The localization of the secretion of ACTH by an adenoma was strongly predicted by the samples at the level of the IPS since the adenoma was found in 8 patients out of 12. We can say that in our series there is a good agreement between the IPS sampling and adenoma discovery during surgery

We analysed the other series of literature, we found that patients with negative preoperative images are associated with a lower remission rate. Bochicchio D [08], Salenave [40], Semple PL[42] Conversely, visualization of the lesion preoperatively on MR imaging has been correlated with a higher rate of remission. Bochicchio, *et al.* [8] analyzed 115 patients with preoperative MR images and found a remission rate of 87.1% in patients in whom the adenoma was identified versus 73.6% in patients with no evidence of tumor. Rees, *et al.* [39] reported 100% surgical remission for 23 patients who underwent TSS and who had an MR imaging study showing a microadenoma, versus 69% of 16 patients with normal findings on MR imaging.

There are studies showing that patients with normal (negative) MR images can obtain very satisfactory rates of remission, including the group with preoperative normal MR imaging in Salenave's study [40]. Our results are far from those reported by Salenav [40], Invitti [23], we found that remission was obtained in 63.63%.

The absence of adenoma on anatomopathological examination was considered to be a predictor of a poor prognosis in other large series; on the other hand in our small series we did not find a big difference since our patients having benefited from a hemihypophysectomy evolved well over at least 03 years of follow-up.

Arnott [3], Oldfield EH [35]. Sheehan JM [44], found that remission rates in patients without histological confirmation of tumor resection range from 36 and 69%. Although some authors did not show a significant difference between outcomes of patients in relation to pathological confirmation of an adenoma, Comtois [14], Yap LB [55]. In the present series, we noted that the presence or absence in preoperatively of the adenoma does not influence the result, since 63.63% of the patients who were in remission had or not an adenoma. which is not in accordance with the results obtained by Invitti, *et al* [23] who found that remission rates were markedly lower in patients in whom an adenoma could not be identified histologically (36 vs75%).

Some factors had a good prognostic of surgical cure in Cushing's disease such as visualization of an adenoma on MRI scan. Histopathological confirmation of an adenoma has been claimed to be a good prognostic factor compared to the absence of confirmation.

In our series, when histological confirmation of tumor and radiological identification of tumor was assessed in combination, (positive findings on histology and radiology) predicted good outcome compared to negative findings for these two investigations. In Chee series the absence of surgical identification of tumor together with negative findings for both histological and radiological assessment predicted a significantly increased risk of failure of treatment.

### Conclusion

Throughout our series and our little experience, it is important to have long-term follow-up in patients with Cushing's disease with normal MRI of the pituitary region to determine the duration of remission.

The success of surgery in Cushing's disease without adenoma visible on pituitary MRI depends mainly on the experience of surgeons and the help provided by the IPSS referral.

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