

Pituitary Magnetic Resonance Imaging Findings Do Not Influence Surgical Outcome in Adrenocorticotropin-Secreting Microadenomas

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The pituitary origin of ACTH secretion in ACTH-dependent hypercortisolism can be difficult to assess, as magnetic resonance imaging (MRI) frequently fails to identify ACTH-secreting microadenomas or, on the contrary, may give false positive images of microadenomas. The choice of therapeutic option for patients with such normal MRI findings is controversial. Some groups propose routinely pituitary surgery, whereas others consider that neurosurgical exploration may be less successful and more harmful, and therefore prefer other types of management. The aim of this study was to compare surgical outcomes between patients with Cushing's disease (CD) and normal vs. positive pituitary MRI findings. Fifty-four patients (44 women and 10 men) with CD, operated on after 1996 in two centers (Kremlin-Bicêtre and Bordeaux) and followed postoperatively during a mean period of 19.9 ± 22.7 months (range, 1–89 months), were enrolled in this retrospective study. Twenty-eight patients had normal pituitary MRI findings, and the pituitary origin of ACTH was established by bilateral petrosal sinus sampling in all of these cases. Twenty-six patients had positive MRI findings clearly showing a microadenoma. The two groups were not significantly different in terms of the sex ratio, age, frequency of hypertension, or diabetes, basal 24-h urinary free cortisol levels and follow-up. All of the patients were operated on by two experienced neurosurgeons using the same surgical protocol. Selective adenectomy was performed when a tumor was identified, and

subtotal hypophysectomy was performed when the lesion was uncertain or when no tumor was found during surgical exploration. Respectively, 50% and 84% of patients with normal and positive MRI results underwent adenectomy ($P < 0.05$). A pituitary adenoma (confirmed by pathological examination) was found at surgery in 53% and 88% of patients in the normal and positive MRI groups, respectively ($P < 0.05$). The early surgical success rate (combining patients with corticotrophic deficiency and patients with eucortisolism) was similar in the normal and positive MRI groups (78% and 88%, respectively; $P = 0.85$). The recurrence rate was lower in the normal MRI group, but the difference did not reach statistical significance (9% vs. 30%; $P = 0.07$). The final remission rate at the last visit was similar in the normal and positive MRI groups (72% and 61%, respectively; $P = 0.29$). Postoperative complications were also similar: 10 patients (36%) with normal MRI and five patients (20%) with positive MRI had at least one postoperative complication (surgical and/or pituitary deficiency; $P = 0.12$). Thus, the outcome of pituitary surgery in CD appears to be similar regardless of whether pituitary MRI shows a microadenoma. We recommend neurosurgical pituitary exploration as the first-line treatment of CD, provided that the pituitary origin of ACTH secretion is confirmed by bilateral petrosal sinus sampling in patients with normal pituitary MRI findings. (*J Clin Endocrinol Metab* 89: 3371–3376, 2004)

CUSHING'S DISEASE (CD) is a potentially life-threatening endocrinopathy with a reported yearly incidence of about one case per million inhabitants (1). CD is characterized by hypersecretion of ACTH, usually from a pituitary microadenoma. CD presents both diagnostic and therapeutic challenges. The pituitary origin of hypercortisolism is difficult to prove despite modern imaging procedures, because ACTH-secreting pituitary microadenomas (the main cause of CD) are not visible by magnetic resonance imaging (MRI) in 36–63% of patients (reviewed in Ref. 2).

Abbreviations: BIPSS, Bilateral inferior petrosal sinus sampling; CD, Cushing's disease; MRI, magnetic resonance imaging; UFC, urinary free cortisol excretion.

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Bilateral inferior petrosal sinus sampling (BIPSS) is the gold standard for establishing the pituitary origin of ACTH secretion, but its value for preoperative location inside the pituitary of otherwise invisible pituitary microadenomas is controversial (2). Surgical excision of ACTH-secreting pituitary microadenomas is notoriously difficult even in experienced hands, and the short-term remission rate ranges from 69–92%. The long-term success rate is even lower, with recurrences of hypercortisolism in 5–20% of cases (reviewed in Refs. 2 and 3). Surgical failure can be due to tiny pituitary adenomas, extrapituitary (ectopic) adenomas, or corticotroph hyperplasia. The influence of preoperative pituitary MRI findings on surgical outcome is also controversial (3–8). Patients with normal MRI findings may undergo more aggressive surgery, with a higher risk of complications. The aim of this study was thus to compare the outcome of

surgery between CD patients with and without MRI-visible microadenomas.

Subjects and Methods

Patients

This retrospective study involved 54 consecutive patients managed at Bicêtre and Bordeaux University hospitals who underwent transsphenoidal adenectomy as primary treatment for CD between 1996 and 2002. Patients with CD, but a macroadenoma, or in whom surgical treatment was not performed as primary treatment were excluded from this study. The population comprised 44 women (mean age \pm SD, 39.4 \pm 14.7 yr; range, 11–74 yr) and 10 men (mean age, 39.1 \pm 13.2 yr; range, 15–56 yr). The median postoperative follow-up was 19.9 \pm 22.7 months (range, 1–89 months).

Preoperative biochemical evaluation

All patients were referred to the participating centers with clinical Cushing's syndrome. The diagnosis of ACTH-dependent Cushing's syndrome was based on the presence of detectable plasma ACTH concentrations in patients with increased 24-h urinary free cortisol excretion (UFC), loss of the circadian plasma cortisol pattern, and failure of low dose dexamethasone (2 mg/d for 48 h) to suppress cortisol secretion (9, 10).

The source of ACTH secretion was initially investigated by pituitary MRI and noninvasive biochemical investigations, such as high dose dexamethasone administration (8 mg/d for 48 h), metyrapone, CRH, and desmopressin stimulation tests (1, 5, 9–11). Patients with abnormal pituitary MRI findings but discordant biochemical results ($n = 11$), and all patients with negative MRI (regardless of the results of biochemistry), underwent BIPSS.

Radiological procedures

MRI. MRI was performed with a superconducting magnet scanner. Before gadolinium injection, the following conventional sequences were obtained in the coronal plane with a slice thickness of 3 mm: T1-weighted spin echo, T2-weighted turbospin echo, followed by coronal dynamic acquisition, beginning simultaneously with gadolinium injection, T1-weighted turbospin echo, and, finally, T1-weighted spin echo (12, 13).

Imaging studies were independently reviewed by the neuroradiologist, at least one endocrinologist, and the patient's surgeon. Full agreement was reached on the positive nature of MRI findings. Otherwise, when MRI appeared normal or interpretation was ambiguous, MRI was considered normal.

BIPSS. The pituitary origin of ACTH was established by simultaneous bilateral IPSS with measurement of central to peripheral ACTH gradients after CRH administration (14, 15). No major adverse events occurred during the procedure.

Surgical procedures

Two surgeons, one in each participating center, operated on the patients managed in their center. Both had extensive experience in pituitary tumor surgery and had received the same specific training with Patrick Derome, Neurosurgery Department, Foch Hospital (Suresnes, France) (16). The same transsphenoidal surgical procedure was used. After opening the sellar floor and sellar dura, the pituitary gland was exposed. When no adenoma was seen at this step, the pituitary gland was cut horizontally, and the entire anterior and posterior lobes were extensively explored. When a tumor was identified, selective adenectomy was performed, with removal of a rim of normal pituitary tissue. When no tumor was reliably identified, the lower two thirds of the pituitary were excised. The day of the operation, all patients received high dose parenteral steroid therapy (100–300 mg hydrocortisone); the dose was rapidly decreased after surgery and was replaced by 20 mg/d oral hydrocortisone after 2–3 d.

Histological and immunocytochemical studies

Pituitary specimens were fixed in buffered 10% formol and embedded in paraffin wax. Four-micrometer sections were prepared and rou-

tinely stained with Herlant's tetrachrome and periodic acid-Schiff orange. Adenoma tissue was identified on the basis of classical criteria, namely the presence of connective tissue, vascular stroma, and neoplastic monomorphous epithelial cells arranged in a diffuse, papillary, or sinusoidal pattern. However, due to the frequently small size of adenomatous tissue and the usual presence of normal pituitary cords, samples were more or less representative of a corticotroph adenoma. Serial sections were thus routinely performed to explore the sample in totality for finding isolated adenomatous cells. Reticulin staining was also performed to improve histopathological diagnosis by differentiating adenomatous and normal pituitary patterns. Immunocytochemical studies were performed as previously described (13, 16). Several commercially available antibodies have been used in this series, such as ACTH-(1–39) [ACTH-(1–24) and ACTH-(17–39)], α MSH, β -endorphin, and lipotropic hormone, but the most reliable was the anti-ACTH antibody, even if most corticotroph adenomas were also immunoreactive for the other three.

Postoperative biochemical evaluation

Biochemical investigations were performed during the first month after surgery and at least 20 h after the previous dose of hydrocortisone. Pituitary function was then assessed at 3 months, every 6 months for 2 yr, and at least yearly thereafter.

Postoperative corticotrophic function was classified as follows. 1) Corticotrophic deficiency was diagnosed if plasma cortisol levels were low (<100 nmol/liter) at 0800 h in the immediate postoperative period and/or if, during follow-up, negative results were obtained in the metyrapone test (peak 11-desoxycortisol, <10 μ g/dl), insulin tolerance test, or CRH test (peak serum cortisol, <550 nmol/liter after stimulation) (5, 17). Replacement therapy with glucocorticoids was pursued at a dose of 20 mg hydrocortisone daily when corticotrophic deficiency was diagnosed. 2) Eucortisolism was defined as normal UFC and positive suppression by low dose dexamethasone (serum cortisol at 0800 h, <75 nmol/liter) (5, 17, 18). Hydrocortisone was discontinued in such cases. 3) Failure or relapse was defined by the persistence or recurrence of hypercortisolism, respectively.

Thyrotrophic function was assessed by measuring free T_4 , free T_3 , and TSH. In women, the gonadotrophic axis was assessed off estrogen and progestin, during the early follicular phase. LH and FSH were measured at baseline and after GnRH administration (100 μ g, iv). Plasma estradiol, testosterone, and Δ^4 -androstenediol were also routinely measured. In men, the gonadotrophic axis was evaluated by testosterone assay (13). Somatotrophic deficiency was not studied in all patients.

Statistical analysis

The χ^2 test was used to compare surgical and pathological findings and postoperative outcomes between patients with normal and abnormal MRI results and between the two centers. Age and follow-up were compared by covariance analysis with Fisher's exact test. $P < 0.05$ was considered statistically significant. StatView 4 software (SAS Institute, Cary, NC) was used for all statistical analyses.

Results

Pituitary MRI

Direct evidence of intrasellar lesions was obtained (definite lesion, >3 mm) in all 26 patients in the positive MRI group. The normal MRI group comprised 28 patients with no visible adenoma on MRI or with only upward bulging of the gland, lateral displacement of the stalk, or an asymmetric sellar floor, but no direct evidence of microadenoma.

The clinical characteristics of the patients within normal MRI and positive MRI groups are shown in Table 1. The two groups were similar in terms of sex ratio, age, frequency of diabetes or hypertension, basal UFC, and follow-up. No significant differences were found between the two centers.

TABLE 1. Basal characteristics of the 54 patients with CD and normal or positive (*i.e.* showing evidence of a microadenoma) pituitary MRI

	Normal MRI	Positive MRI	P
No. of patients	28	26	
Sex ratio (M/F)	8/20	2/24	NS
Mean age (range)	38.4 (11–62)	40.4 (14–74)	NS
Median follow-up in months (range)	21 (1–89)	18.1 (1–72)	NS

NS, Nonsignificant.

Neurosurgical procedures and histopathological findings

In the positive MRI group, an adenoma was found by the neurosurgeon, and selective adenomectomy was performed in 22 patients (84%). The presence of an adenoma was confirmed pathologically in 21 (95%) of these 22 patients. In the four remaining patients (16%), subtotal hypophysectomy was performed. The presence of an adenoma was confirmed pathologically in two of them.

In the normal MRI group, an adenoma was identified by the neurosurgeon in 14 (50%) of the 28 patients. When selective adenomectomy was performed, pathological examination confirmed the presence of an adenoma in 10 (71%) of these 14 patients. The presence of adenomatous tissue was confirmed on pathological specimens in 5 (35%) of the remaining 14 patients who had no evidence of microadenoma during surgical exploration and who underwent subtotal hypophysectomy (Table 2). Regardless of the surgical procedure, pathological identification of an ACTH-secreting pituitary microadenoma was less frequent in the normal MRI group than in the positive MRI group (respectively, 15 of 28 patients, 53%; and 23 of 26 patients, 88%; $P < 0.05$).

Impact of neurosurgery on CD

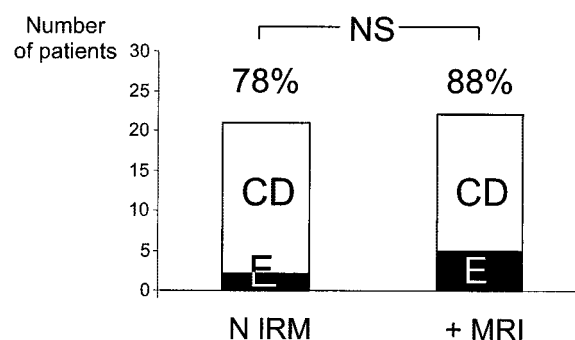
Immediate postoperative outcome. The first postoperative biochemical tests were performed during the first month in 52 of the 54 patients and within 3 months in the other two patients (one in each group). Corticotrophic deficiency was observed in 17 (68%) of 25 patients and in 19 (70%) of 27 patients in the positive and normal MRI groups, respectively ($P = 0.77$). Seven patients (two with normal MRI and five with positive MRI) were eucortisolic, whereas hypercortisolism persisted in nine patients (six with normal MRI and three with positive MRI). Overall, the immediate postoperative remission rate (*i.e.* the total number of patients with corticotrophic deficiency or eucortisolism) was similar in the two groups (21 of 27 patients, 78%; 22 of 25 patients, 88%; in the normal and positive MRI groups, respectively; $P = 0.85$; Fig. 1).

Recurrences. During a median follow-up of 19.9 months, hypercortisolism recurred in nine (19.5%) of the 46 patients who were considered to be in remission at the initial postoperative evaluation (five were initially eucortisolic, and four had corticotrophic deficiency). Two (9%) of these nine patients were in the normal MRI group, and seven (30%) were in the positive MRI group. Recurrences tended to be less frequent in the normal MRI group ($P = 0.07$).

TABLE 2. Comparison of surgical procedure and histopathological findings between patients with normal or positive (*i.e.* showing evidence of a microadenoma) pituitary MRI

	Normal MRI	Positive MRI	P
Adenomectomy	14/28 (50)	22/26 (84)	<0.01
Adenomectomy and positive histopathology	10/14 (71)	21/22 (95)	0.13
Subtotal hypophysectomy	14/28 (50)	4/26 (15)	<0.01
Subtotal hypophysectomy and positive histopathology	5/14	1/4	
Total no. of patients with positive histopathology	15/28 (53)	23/26 (88)	<0.01

Percentages are given in parentheses.

**FIG. 1.** Comparison of outcome at early postoperative evaluation of corticotrophic function in patients with CD ($n = 52$) and normal or positive (*i.e.* showing evidence of a microadenoma) pituitary MRI.

Final biochemical evaluation and final remission rate. Corticotrophic status remained stable during follow-up in nine (47%) of the 19 patients with normal MRI and in six (35%) of the 17 patients with positive MRI who had corticotrophic deficiency at the initial postoperative evaluation. Eleven patients with normal MRI and 10 patients with positive MRI were eucortisolic at the last visit. The global remission rate (sum of patients with corticotrophic deficiency and patients with eucortisolism) was similar in the normal MRI group (20 of 28 patients, 72%) and in the positive MRI group (16 of 26 patients, 61%; $P = 0.29$; Fig. 2). Kaplan-Meier analysis showed no difference in the cumulative survival rate (patients free of disease) between the two groups (Fig. 3). No correlation was found between histological findings (presence or absence of a microadenoma) and remission rate in subgroup (positive MRI or normal MRI groups) analysis, whereas there was a positive correlation between histological findings and remission rate when analysis was performed on the entire population.

Postoperative complications

No postoperative deaths occurred.

The frequency of postoperative complications and pituitary deficiency was not significantly different between the two groups. Cerebrospinal fluid leakage, without meningitis, occurred in one patient in each group. It was related to the presence of an ectopic adenoma (along the pituitary stalk) in the patient with positive MRI, and in the other patient (normal MRI) necessitated reoperation, leading to panhypopituitarism and permanent diabetes insipidus. Apart from this

case, permanent diabetes insipidus occurred in one patient in each group.

Panhypopituitarism also occurred in a patient with normal MRI who underwent subtotal hypophysectomy. Isolated gonadotropic deficiency and thyrotropic deficiency occurred in, respectively, two and four patients with normal MRI and in two and two patients with positive MRI. These events were not related to the surgical procedure: subtotal hypophysectomy and selective adenomectomy were performed in two and eight cases, respectively. Overall, 10 patients with normal MRI (36%) and five patients with positive MRI (20%) had at least one complication ($P = 0.12$).

No significant difference between the two centers was found in terms of patient characteristics, duration of follow-up, or the rates of remission, complications, or hypopituitarism.

Discussion

This study suggests that therapeutic and morbid outcomes of surgery for CD do not differ according to the presence or absence of visible microadenomas on preoperative pituitary MRI. MRI is a widely used tool for differential diagnosis of ACTH-dependent Cushing syndromes along with biochemical suppression and stimulation of the HPA axis. However, ACTH-secreting microadenomas are frequently not visible on MRI in patients with Cushing disease (36–63% of cases)

(reviewed in Ref. 2), whereas false positive MRI signs of microadenoma may be seen in at least 10% of normal subjects (19). The optimal therapeutic approach to patients with normal MRI is controversial. A lower success rate of pituitary neurosurgery in patients with CD and normal MRI was found by the European Cushing's Disease Survey Group (3). Other investigators have concluded that neurosurgical exploration is associated with more complications in these patients (6, 7). Some researchers have even suggested that neurosurgical exploration is not indicated for patients with CD and normal MRI (4). However, contrary to other therapeutic options [radiotherapy, bilateral adrenalectomy, and 1,1-dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)-ethane], pituitary neurosurgery can potentially cure these patients, obviating the need for hormone replacement therapy. As there is no clear evidence that, with time, ACTH-secreting pituitary microadenomas become visible by MRI, while hypercortisolism is controlled with agents such as ketoconazole, early pituitary surgery in these patients with normal MRI is advocated by other authorities. Moreover, no difference in the remission rate after surgery has been found according to whether a microadenoma is visible on pituitary images (5, 6, 8). However, firm conclusions are difficult to draw from these studies in which different imaging techniques (computed tomography or MRI) were used, patients with macroadenomas were also included, BIPSS was not systematically performed to rule out ectopic ACTH secretion, and different definitions were used (3–6, 8). This prompted us to retain for our study only recently treated patients with pituitary microadenoma who had had modern MRI techniques (after 1996) and in whom BIPSS was routinely performed when MRI was normal.

The surgical procedure used in this study was highly standardized and was the same regardless of whether a microadenoma was visible by MRI. It should be pointed out that the two neurosurgeons obtained similar results. Selective adenomectomy was performed when a microadenoma was found during surgical exploration. This was less frequent when MRI was normal (50%) than when MRI was positive

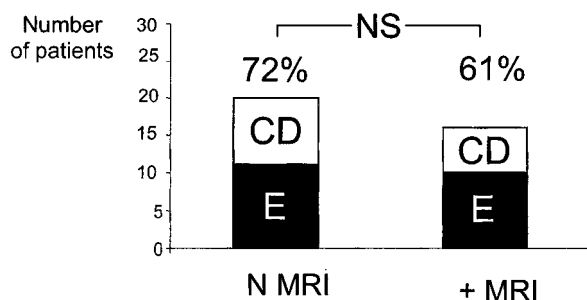
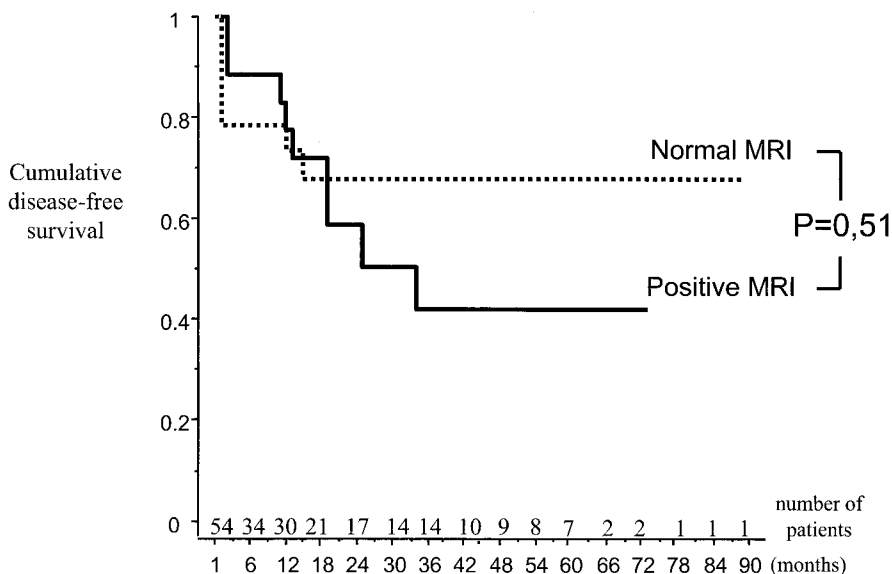


FIG. 2. Comparison of outcome at the last evaluation visit in patients with CD ($n = 54$) and normal or positive (*i.e.* showing evidence of a microadenoma) pituitary MRI.

FIG. 3. Cumulative disease-free survival rate of CD after pituitary surgery according to preoperative pituitary MRI (normal or positive, *i.e.* showing evidence of a microadenoma) by Kaplan-Meier analysis.



(84%). However, even when the neurosurgeon was sure he had removed an adenoma and thus had performed a selective adenomectomy, histological confirmation was obtained in only 71% of patients with normal MRI (compared with 95% of patients with positive MRI findings). Similar findings have been reported by Buchfelder *et al.* (20). Our results are also similar to those of previous studies showing that regardless of the imaging modality, surgical exploration was often successful, with an adenoma being histologically confirmed in 70–90% of cases (7, 8, 16, 21–23). In our series, regardless of the type of surgery (adenomectomy or subtotal hypophysectomy), histological examination was less frequently positive when MRI was normal. The absence of adenoma on pathological examination has been considered a factor of poor prognosis (24–26). However, in our series the remission rate was similar whether pathological examination was positive or negative. Remission of CD despite negative pathological examination may be due to postoperative ischemic necrosis of an adenomatous remnant, fortuitous aspiration of a tiny (millimetric) adenoma during surgery, or false negative pathological examination (27). No evidence of pituitary corticotroph hyperplasia was found in our series.

Immediate postoperative outcome was similar in the two groups of MRI findings (72% and 61% of patients with normal and positive MRI findings, respectively). These results are in keeping with previously published data (3, 5, 7, 8, 16, 17, 21–23). They also validate the use of selective adenomectomy when an adenoma is found and of subtotal hypophysectomy when no obvious adenoma is found, rather than total hypophysectomy, removal of the central wedge, or hemihypophysectomy (15, 20, 28), which have not given better success rates (29, 30). During follow-up, the global recurrence rate was 19.5% (nine of the 46 patients who were in remission postoperatively). The recurrence rate is highly variable in recently reported series (5–21%) (reviewed in Ref. 5). Recurrences tended to be less frequent in the normal MRI group than in the positive MRI group. This is in accordance with the results of the European Multicenter Study (3), whose authors concluded that identification and removal of pathological tissue during surgery were easier when a microadenoma was visible on MRI (perhaps because the microadenoma was larger). However, for the same reasons, positive MRI seems to be associated with a higher risk of remnant adenomatous cells (3, 31).

Among the nine patients in our series who relapsed (two with normal MRI and seven with positive MRI), five were eucortisolic at initial postoperative evaluation. Only two of the seven patients who were eucortisolic at the postoperative evaluation did not relapse. This confirms previous conclusions (3, 17, 30) that the likelihood of recurrence is higher when patients are eucortisolic than when they are corticotropin deficient early after surgery. However, long-lasting remissions have also been reported in eucortisolic patients (18, 26, 32). In four patients, despite corticotropin deficiency early after surgery (cortisol at 0800 h, <50 mmol/liter), recurrence was observed after a median follow-up of 18 months. In contrast, Trainer *et al.* (17) observed no recurrences among patients with postoperative corticotrophic deficiency, possibly because this series was smaller than ours (20 patients).

Neurosurgery may need to be more aggressive when preoperative MRI is normal. In our series, subtotal hypophysectomy (removal of two thirds of the pituitary) was performed in 50% of patients with normal MRI and only 15% of patients with positive MRI. Semple *et al.* (6, 7) also reported higher immediate surgical complication and mortality rates in patients with normal MRI (22%; despite adenomectomy in 78% of cases) or with macroadenoma (31%) than in patients with visible microadenoma (6.7%). In our series the complication rate was similar regardless of MRI findings and the neurosurgical procedure. Pituitary deficiencies tended to be more frequent in patients with normal MRI than in patients with visible microadenoma (28% *vs.* 15%, respectively). Independently of imaging results, the reported rate of hypopituitarism (at least one deficient pituitary hormone axis) ranged from 14–89% (reviewed in Ref. 8). Postoperative pituitary deficiency rates have rarely been analyzed according to the results of preoperative imaging. We are aware of only one such study (8) in which patients with normal or inconclusive preoperative computed tomography/MRI had a higher risk of pituitary deficiency (hypothyroidism in 81% of cases) than patients with imaging signs of a microadenoma (35%). These differences are probably due to the use of more aggressive surgical procedures (35% of patients had total hypophysectomy) than in our series. Indeed, in general, the pituitary deficiency rate is related to the aggressiveness of surgery. Trainer *et al.* (17) reported panhypopituitarism in more than 80% of patients after total hypophysectomy, whereas hypothyroidism was found in 10% and 16% of patients, and hypogonadism in 50% and 9% of patients, after hemihypophysectomy and microadenomectomy, respectively. The adverse effects of subtotal hypophysectomy have not previously been reported.

Interpretation of our negative results may be cautious due to the lack of power of our study. However, when considering the very low incidence of the disease, reaching a satisfactory power will probably be difficult unless studies involving a much higher number of patients are performed.

In conclusion, MRI remains highly useful as part of the diagnostic procedure and may avoid the need for BIPSS if biochemical tests support the diagnosis of CD. Moreover, MRI can help the surgeon during pituitary exploration, leading to less aggressive surgery and fewer complications. Nevertheless, in the hands of highly trained pituitary surgeons, the efficacy and morbidity of pituitary neurosurgery in patients with CD appear to be identical regardless of whether a microadenoma is visible on preoperative MRI. Thus, if the pituitary origin of ACTH secretion is established by BIPSS in patients with normal MRI findings, we recommend pituitary neurosurgery as the first-line treatment for CD. An approach based on selective adenomectomy when an adenoma is found during surgical exploration, and two thirds inferior hypophysectomy when no adenoma is found, offers an acceptable risk-benefit ratio in this setting.

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