Corticotroph Tumor Progression after Adrenalectomy in Cushing’s Disease: A Reappraisal of Nelson’s Syndrome

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Context: Adrenalectomy is a radical treatment for hypercortisolism in Cushing’s disease. However, it may lead to Nelson’s syndrome, originally defined by the association of a pituitary macroadenoma and high plasma ACTH concentrations, a much feared complication.

Objective: The objective of the study was to reconsider Nelson’s syndrome by investigating corticotroph tumor progression based on pituitary magnetic resonance imaging scan and search for predictive factors.

Design: This was a retrospective cohort study.

Setting: The complete medical records of Cushing’s disease patients at Cochin Hospital were studied.

Patients: Patients included 53 Cushing’s disease patients treated by adrenalectomy between 1991 and 2002, without previous pituitary irradiation.

Measurements: Clinical data, pituitary magnetic resonance imaging data, and plasma ACTH concentrations for all patients and pituitary gland pathology data for 25 patients were recorded. Corticotroph tumor progression-free survival was studied by Kaplan-Meier, and the influence of recorded parameters was studied by Cox regression.

Intervention: There was no intervention.

Results: Corticotroph tumor progression ultimately occurred in half the patients, generally within 3 yr after adrenalectomy: A shorter duration of Cushing’s disease (adjusted hazard ratio: 0.899/yr), and a high plasma ACTH concentration in the year after adrenalectomy (adjusted hazard ratio per 100 pg/ml (22 pmol/liter): 1.069) were predictive of corticotroph tumor progression. In one case, corticotroph tumor progression was complicated by transitory oculomotor nerve palsy. During follow-up, corticotroph tumor progression was associated with the increase of corresponding ACTH concentrations (odds ratio per 100 pg/ml of ACTH variation: 1.055).

Conclusion: After adrenalectomy in Cushing’s disease, one should no longer wait for the occurrence of Nelson’s syndrome: modern imaging allows early detection and management of corticotroph tumor progression. (J Clin Endocrinol Metab 92: 172–179, 2007)
have never been demonstrated to be predictive of NS, including sex (7, 9, 21, 25), plasma ACTH concentration before adrenalectomy (12, 21, 25, 26), dose of glucocorticoid substitution treatment after adrenalectomy (7, 12, 14), and pregnancy (13).

Complications related to NS are essentially due to tumor growth: definitive or transitory chiasmatic compression with visual field loss is the most frequent, with a prevalence of 1:10 to 4:9 (7–11, 13–16, 18, 19, 22, 27). Oculomotor nerve palsy has also been described (19), as has tumor necrosis with sudden intracranial hypertension (8, 13). Diabetes insipidus (5) and hypopituitarism are rare. Malignant pituitary tumor with distant metastases has occasionally been described (9, 13). Finally, exceptional gonad tumors consisting of hyperplastic ectopic adrenocortical tissue have also been described (28–31).

However, all these studies are subject to several major limitations: 1) pituitary macroadenoma was diagnosed by sellar x-ray tomography or on the basis of visual defects or was not even considered, 2) high levels of ACTH secretion were defined based on a qualitative assessment of cutaneous pigmentation or on various arbitrary cut-off points for plasma ACTH concentration, and 3) the cohorts of patients received different treatments, some of which may have directly interfered with pituitary tumor growth. Pituitary radiotherapy is one such treatment. Finally, major technical advances, such as transsphenoidal surgery and pituitary magnetic resonance imaging (MRI), occurred during the inclusion periods for these studies. Consequently, data from these series are difficult to interpret, compare, and transpose to modern clinical practice.

The aim of this study was to reconsider NS by separately considering corticotroph tumor progression and the variations of plasma ACTH concentration after adrenalectomy in Cushing’s disease. Corticotroph tumor progression was assessed by pituitary MRI. We report its incidence, predictive factors, complications, and predictability between two consecutive MRIs based on the corresponding ACTH concentrations for a cohort of patients from a single center, who had never undergone pituitary radiotherapy, during a period in which medical procedures did not change.

**Patients and Methods**

**Patients**

The series consisted of 59 consecutive patients with Cushing’s disease followed at the Endocrinology Department of Cochin Hospital (Paris, France), who underwent adrenalectomy between February 1991 and October 2002. These patients are part of a cohort of about 400 patients with Cushing’s disease followed up during the same period in our institution. Pituitary surgery is most often the first-line treatment, and anticoagulant treatment, usually 1,1-dichlorodiphenyl dichloroethane (p,p-DDD), is most often proposed in case of failure or recurrence. Pituitary irradiation is restricted to tumors with evidence of locoregional aggressiveness. Adrenalectomy is proposed when the likelihood of a successful pituitary surgery is low (unresectable adenomas, previous failures, no visible adenoma on repeated pituitary MRIs) and when anticoagulant medication is not indicated (inefficiency, desire of pregnancy, intolerance) or in rare cases of life-threatening forms of hypercortisolism in the absence of visible adenoma at pituitary MRI.

Of the 59 patients who underwent adrenalectomy, five were excluded because pituitary irradiation was performed before or at the time of adrenalectomy. One additional patient was excluded because of remnant macroprolactinoma at the time of adrenalectomy, in the context of multiple endocrine neoplasia 1 syndrome. None of the remaining patients underwent any pituitary irradiation before adrenalectomy. All underwent pituitary MRI before adrenalectomy, in a median interval of 3.8 months. Of note this interval was longer than 7 months for three patients: 15 months for a patient who had two negative pituitary MRIs; 15 months for a patient who had two negative pituitary MRIs and an unsuccessful pituitary surgery; 24 months for a patient with remaining hypercortisolism after two pituitary surgeries followed by 10 yr of negative pituitary imaging.

In the remaining 53 patients, ACTH-dependent Cushing’s syndrome was diagnosed before adrenalectomy as being Cushing’s disease, to various levels of certainty, and patients were classified into four diagnostic groups: 1) group 1 (n = 22): direct evidence of pituitary adenoma (pathological confirmation of basophilic adenoma with ACTH immuno- positivity in 18 patients or corticotropic insufficiency after pituitary surgery despite no pathological confirmation in four patients); 2) group 2 (n = 14): a significant central to peripheral gradient of ACTH on bilateral inferior petrosal sinus sampling (n = 3) or a positive ACTH/cortisol response to CRH stimulation (n = 11); 3) group 3 (n = 11): a concordant positive response to two classical dynamic tests: high-dose dexamethasone suppression test, associated with either the metyrapone test, or lysine-vasopressin stimulation; or 4) group 4 (n = 6): a positive high-dose dexamethasone suppression test alone (n = 4) or no dynamic test performed due to immediate adrenalectomy for life-threatening forms of the disease (n = 2).

All patients underwent clinical examination and had a chest x-ray showing no evidence of thoracic tumor.

For each patient, the following clinical criteria were recorded: sex, age at adrenalectomy, and duration of Cushing’s disease before adrenalectomy according to anamnesis.

After adrenalectomy, hormone replacement consisted of 9α-fluoro- hydrocortisone (50–100 μg/d) and hydrocortisone (20–30 mg/d) divided in 0800 and 1200 h doses.

**Pituitary MRI evaluation**

All patients underwent pituitary MRI before adrenalectomy and yearly after adrenalectomy (median interval between scans: 12.4 months).

A double reading of the pituitary MRIs was performed: for each patient, all pituitary MRIs were analyzed retrospectively at the same time, in chronological order, by a single senior radiologist (H.B.), with no information on clinical and biological outcome. The results were compared with those obtained at the time at which the MRI scans were actually performed. In cases of discrepancy, a third reading was carried out by two senior radiologists.

Pituitary MRI scans were performed with coronal and sagittal T1 weighting, with and without enhancement and with coronal T2 weighting.

Corticotroph tumor progression was defined as the occurrence of an adenoma in cases in which no adenoma was visible on previous MRI scans or by the progression of an existing adenoma (Fig. 1).

The presence of an adenoma on pituitary MRI was detected based on:
1) direct evidence of a microadenoma, confirmed on the following MRI; or 2) presence of an image compatible with a microadenoma, associated with at least one of these indirect signs (pituitary stalk deviation, or upward convexity of the diaphragma sellae, or sella floor asymmetry) in cases in which the pituitary gland was heterogeneous and confirmed on the following MRI.

The absence of an adenoma was recorded if these criteria were not met.

The progression of an existing adenoma was defined as an increase of at least 2 mm in one of the three dimensions of the adenoma, associated with at least one of the three following features: 1) increase in pituitary stalk deviation, or upward convexity of the diaphragma sellae; or 2) increase in sellar floor asymmetry.

For the last pituitary MRI before adrenalectomy, the presence or absence of a pituitary adenoma was recorded. After adrenalectomy, each MRI was systematically compared with the previous scan for the evaluation of corticotroph tumor progression.
Corticotroph tumor progression was defined as a lack of increase in the size of an adenoma visible before adrenalectomy (C). B, Lack of corticotroph tumor progression was defined as the absence of adenoma (D) if no adenoma was visible before adrenalectomy (A) or as an increase in the size of an adenoma (D) visible before adrenalectomy (A) or as the absence of adenoma (D) if no adenoma was visible before adrenalectomy (C).

**Hormone measurements**

We used the mean of several samples (median of two samples) collected on consecutive days (mean of 1.2 d) at 0800 h, 20 h after the last administration of glucocorticoid, to optimize our evaluation of baseline plasma ACTH concentration (32). Cortisol concentration was determined at the same time.

ACTH was assayed by immunoradiometric assay (ELSA-ACTH, Cis Bio International, Gif-sur-Yvette, France). Cortisol was assayed by competition assays (CORT-CT2; Cis Bio International until 2001, and then IMMULITE 2000 Cortisol; Diagnostic Products Corp., Los Angeles, CA). All dynamic tests were performed as previously described (33).

During the follow-up, for each patient, baseline plasma ACTH and cortisol concentrations were recorded regularly, about once per year (median interval 11.8 months) after adrenalectomy.

Some patients had received o,p’DDD at some time in the course of their disease, before adrenalectomy. Evidence of cortisol deprivation was provided by clinical improvement associated with decrease of at least 50% in 24-h urinary cortisol in the year after o,p’DDD introduction with respect to the value obtained six months previously.

**Pathological analysis**

Pathological slides of pituitary tissue were available for 25 of the 28 patients who had undergone transsphenoidal surgery before adrenalectomy. These slides were analyzed retrospectively by a single pathologist (M.K.). Standard staining included periodic acid-Schiff, Herlant’s tetrachrome, and hematoxylin-eosin. Immunostaining was performed retrospectively for the study with anti-Ki67 (1:100; Dako, Trappes, France) and anti-ACTH (1:1000; Dako) antibodies. The size of the samples was estimated by the number of high-power fields. This number was greater than 25 for 17 patients, between 5 and 25 for seven patients, and less than 5 for one patient. This pathological review was carried out blind to the patient’s clinical outcome and the results of the first pathological analysis.

The following criteria were recorded: the presence of an adenoma composed of corticotroph cells (ascertained by their basophilic aspect with positive ACTH immunostaining), the presence of mitoses (yes or no), and the presence of Ki67-immunopositive nuclei (yes or no).

**Statistical analysis**

The primary end point was corticotroph tumor progression, with follow-up starting at adrenalectomy. Corticotroph tumor progression-free survival rates were estimated by the Kaplan-Meier method (34). The predictive value of clinical, morphological, biological, and pathological criteria for corticotroph tumor progression was evaluated using Cox’s proportional hazards regression model (35).

The relationship between corticotroph tumor progression observed at an MRI scan and ACTH concentration collected at the same time was evaluated by logistic regression analysis (a multilevel model was used to account for the clustering effect of patients because patients had undergone several determinations of ACTH concentration, and interindividual variation may have occurred).

**Results**

**Patients**

Fifty-three patients with Cushing’s disease who were followed up at the same center and had not received pituitary irradiation underwent adrenalectomy between February 1991 and October 2002. Clinical, morphological, biological, and pathological features are summarized in Table 1.

The decision to perform adrenalectomy was made on a case-by-case basis: 1) after failure of pituitary surgery in 28 cases (10 immediate failures, 18 recurrences), 2) after the withdrawal of anticortisol treatment in the absence of a pituitary adenoma on MRI in 22 cases (13 recurrences, seven intolerances, three intended pregnancies), or 3) as a first-line treatment in life-threatening forms of the disease in two cases.

Twenty-eight patients underwent pituitary surgery before adrenalectomy: pathological evidence of a corticotroph adenoma was obtained in 18 patients (64%), with another four patients (14%) displaying corticotroph insufficiency after surgery despite negative pathological examinations [early morning plasma cortisol less than 10 ng/ml (27.5 nmol/liter) in three and 50 ng/ml (138 nmol/liter) in the fourth; these four patients had recurrent hypercortisolism between 10 and 60 months after surgery]. We also counted mitoses and Ki67-immunopositive nuclei (Table 1).

The last pituitary MRI before adrenalectomy showed no evidence of adenoma in 46 patients (87%). Adenoma was detected in seven patients (13%): two displayed cavernous involvement and four were not considered to have an adenoma on MRI at the time of adrenalectomy, but the presence of an adenoma was confirmed by retrospective analysis of this scan. Of note, four of these patients had previously undergone pituitary surgery.

Of note, none of the patients presented any pituitary insufficiency at the time of adrenalectomy, apart in some cases with cortisol-induced functional hypogonadotropic hypogonadism.
ACTH concentration after adrenalectomy

In the year after adrenalectomy, early-morning plasma ACTH concentrations measured 20 h after the last glucocorticoid administration were between 41 and 3840 pg/ml (9 and 845 pmol/liter), with a median of 424 pg/ml (93 pmol/liter). Corresponding cortisol values were between 0 and 51 ng/ml (0 and 140 nmol/liter), with a median of 0. The values for each patient are given in Table 2.

Corticotroph tumor progression after adrenalectomy

The median duration of follow-up after adrenalectomy was 4.6 yr (range 0.5–13.5). Kaplan-Meier curve for corticotroph tumor progression-free survival is presented in Fig. 2. Three years after adrenalectomy, the proportion of patients presenting corticotroph tumor progression reached 39%; this proportion tended toward a plateau at 47% after seven years.

Factors predictive of corticotroph tumor progression (Table 3)

Univariate and multivariate analyses were performed to identify factors predictive of corticotroph tumor progression. Univariate analysis showed that a shorter duration of Cushing’s disease, the presence of an adenoma on pituitary MRI at adrenalectomy, and a high plasma ACTH concentration in the year after adrenalectomy were significant predictive factors for corticotroph tumor progression (Table 3). Of note, none of the corticotroph adenoma pathological features could predict corticotroph tumor progression.

Increases in plasma ACTH concentration during o,p’DDD-induced cortisol deprivation tended to predict corticotroph tumor progression but this relationship did not reach full significance (P = 0.08).

In multivariate analysis, only the short duration of the Cushing’s disease and the high plasma ACTH concentration in the first year after adrenalectomy were found to be independent predictive factors for corticotroph tumor progression (Table 3).

Complications of corticotroph tumor progression

Complete information about the evolution and specific treatments for each patient is given in Table 2. At the time when corticotroph tumor progression was first diagnosed, 17 patients presented microadenoma (81%), and four patients (19%) presented macroadenoma (largest diameter > 10 mm); these last four patients had a visible pituitary adenoma at the time of adrenalectomy. One patient displayed tumor necrosis with transient oculomotor nerve palsy, a complication directly associated with pituitary tumor burden. No patient presented visual field defects, anterior pituitary insufficiency, or diabetes insipidus.

Two patients of the series died: one presented acute myeloblastic leukemia, and the other died suddenly for unknown reasons.

Association between corticotroph tumor progression and ACTH concentration at each MRI scan during the follow-up

Corticotroph tumor progression was evaluated between each couple of consecutive MRIs in the follow-up after ad-
### TABLE 2. Description of corticotroph tumor progression

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ADX, Adrenalectomy; TSS, transphenoidal surgery; Rx, radiotherapy.

<sup>(1)</sup> Symbols describing corticotroph tumor progression: each symbol represents the evolution of pituitary adenoma after adrenalectomy. Triangles (▲) represent corticotroph tumor progression. Squares (●) represent the absence of corticotroph tumor progression. Underlined symbols represent macroadenomas.

<sup>(2)</sup> Specific treatments: the time when TSS was performed is figured by the asterisk (*) symbol in the corticotroph tumor progression after adrenalectomy and radiotherapy by the (#) symbol.
renalec
tomy (Table 2). Corresponding early-morning ACTH concentrations were checked for their association to cortico-
troph tumor progression. To identify the best way to inter-
pret these ACTH concentrations, four simple models were
tested: 1) the absolute ACTH variation between consecutive
MRIs, 2) the relative ACTH variation between consecutive
MRIs, 3) the ACTH concentration concomitant to the first of
consecutive MRIs, or 4) and the ACTH concentration con-
comitant to the second of consecutive MRIs. The absolute
ACTH variation between consecutive MRIs gave the stron-
gest association to corticotroph tumor progression (logistic
regression: odds ratio, 1.055 per 100 pg/ml (22 pmol/liter) of
ACTH variation, 95% CI, 1.023–1.089,  \( P < 0.001 \)).

**Discussion**

This study provides an original view of what has long been
known as NS, based for the first time on the fine evaluation
of corticotroph tumor progression rather than on the mere
presence of a pituitary adenoma and high ACTH concen-
tration. This evaluation is based on robust, modern imaging,
by pituitary MRI, and the independent assessment of corti-
cotroph tumor progression and variations in ACTH concen-
tration. This study is subject to two major limitations: it is
retrospective and the number of patients included is small.
However, the patients were followed up at a single center,
using the same techniques throughout the observation
period.

Particular efforts were made to confirm the diagnosis of
Cushing’s disease in this retrospective study. Despite abso-
lute proof of corticotroph adenoma, *i.e.* the pathological doc-
umentation of a corticotroph adenoma, is provided for only
26 patients (18 before adrenalectomy and eight after adre-
alectomy), it seems unlikely that patients from the series
actually had an occult ectopic ACTH syndrome for several
reasons: 1) for the 47 patients in diagnostic groups 1, 2, and
3, the diagnostic tests used have a specificity of 80–100% (36),
2) for group 4, the *a priori* probability of Cushing’s disease
was 80% or more for four of the six patients, 3) after adre-
alectomy, no correlation was found between the diagnostic
groups and corticotroph tumor progression (data not
shown), and 4) no ectopic tumor was documented in any
patient, including the three patients of group 4 without corti-
cotroph tumor progression who underwent chest computed
tomography scans. Finally, for 12 patients with corti-
cotroph tumor progression but not operated during the
follow-up period, an expanding process other than the cor-
ticotroph adenoma cannot be ruled out with certainty. How-
ever, besides few case reports in the context of Cushing’s
disease (37, 38), the incidence of such events is extremely
rare, and none of the patients in this series presented any
predisposing condition such as multiple endocrine neoplasia
I. Moreover, complete hormonal exploration ruled out any
associated secreting pituitary adenoma.

The overall incidence of corticotroph tumor progression
was higher in this study than previously reported for NS (7).
This higher incidence probably results from the higher sen-
sitivity of MRI than of sellar x-rays and computed tomog-
raphy scans. MRI can thus detect small pituitary adenomas
and small changes in adenoma volume, facilitating the early
diagnosis of progressing tumors, and effective treatment to
prevent late complications (39). However, despite the sen-
sitivity of MRI, about half the patients showed no evidence
of corticotroph tumor progression in the first decade after
adrenalectomy.

In most cases, corticotroph tumor progression was first
diagnosed within 3 yr of adrenalectomy, suggesting that
patients may be monitored more closely in the first few years
after surgery. However, because corticotroph tumor pro-
gression can begin later, a lifelong close follow-up with re-
peated pituitary MRIs should probably be recommended.

We found that a shorter duration of Cushing’s disease
before adrenalectomy and a high plasma ACTH concentra-
tion in the year after adrenalectomy were independent pre-
dictive factors for corticotroph tumor progression. The duration of the disease was found to be predictive in a previous study (14), and it may be that patients with long-term disease present small, slowly progressing adenomas, whereas patients with short-term disease present rapidly growing and invading adenomas. Molecular mechanisms differentiating these two kinds of adenomas are poorly documented: a case of somatic glucocorticoid receptor mutation has been reported (40). Plasma ACTH concentration after adrenalectomy is the best documented predictive factor for NS (7, 12–14, 20, 22, 26). Higher ACTH concentrations may correspond to larger pituitary adenomas, for which it may be easier to detect variations. However, the link between high values of ACTH concentration on o,p'DDD needs to be investigated further as a potential cheap, easy-to-calculate marker of corticotroph tumor progression.

In conclusion, corticotroph tumor progression is not constant but occurs early and is predictable. From this study, it appears that in most patients, tumor growth had no clinically detectable consequences and was treatable, at least in the first decade after adrenalectomy. In the absence of specific anti-
corticotroph tumor treatments (41), our data on corticotroph tumor progression should help doctors to decide whether to perform adrenalectomy in cases in which treatments targeting the pituitary gland have failed or do not seem to be indicated (42). Indeed, patients with a Cushing’s disease of recent onset, those with a visible adenoma at MRI, and probably those with exaggerated ACTH retort under o,p’DDE-induced cortisol deprivation are at higher risk of developing corticotroph tumor progression. Recent progress toward understanding the pathogenesis of pituitary tumors (43, 44) and the use of modern, highly sensitive diagnostic tools have radically changed our view (Fig. 3): rather than waiting for NS to develop, we can now closely monitor the possible occurrence of corticotroph tumor progression.

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References

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