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. Cortico-

troph 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: 0.884/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)

I N 1958 NELSON *et al.* (1) first reported the concomitant occurrence of pituitary macroadenoma and high plasma ACTH concentration in a patient treated by total bilateral adrenalectomy (hereafter referred to simply as adrenalectomy) for Cushing's syndrome. Similar cases were subsequently reported (2–5). These observations provided new clues to the pathogenesis of Cushing's disease. They also raised the fear that adrenalectomy could induce or trigger the growth of a pituitary adenoma, with a risk of subsequent complications related to tumor burden. In 1960 Nelson *et al.* (6) reported the first series of such patients: Nelson's syndrome (NS) was born. Fifty years later, however, this condition remains ill defined.

About 50 series of NS cases have been published. NS is

grossly defined as the association of an expanding pituitary tumor and a high ACTH concentration after adrenalectomy in patients with Cushing's disease. The prevalence of NS varied between 8 and 29% in the largest series (7–27), with a time interval between adrenalectomy and NS diagnosis of 0.5–24 yr.

Many studies have tried to identify predictive factors. High baseline plasma ACTH concentration in the year after adrenalectomy is the best validated predictive factor (7, 12–14, 20, 22, 26), but no unique threshold value can be defined. Other predictive factors have been proposed, including young age at adrenalectomy in some studies (9, 15, 21, 24) but not all (7, 25), a lack of pituitary irradiation before adrenalectomy in some studies (7, 22) but not all (9, 16, 19, 25, 26), a surgically or morphologically documented pituitary adenoma before adrenalectomy (22, 25, 26), an invasive pituitary tumor before adrenalectomy (27), the absence of adrenal remnant in some studies (16) but not all (7), the duration of Cushing's disease in some studies (14) but not all (7, 9, 20, 21), and a high urinary cortisol excretion before adrenalectomy in some studies (7, 25) but not all (12, 14, 26). Some factors

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 anticortisolic treatment, usually 1,1-dichlorodiphenildichloroethane (o,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 anticortisolic 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 I 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 immunopositivity in 18 patients or corticotroph 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-fluorohydrocortisone (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; 2) increase in the upward convexity of the diaphragma sellae; or 3) 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.
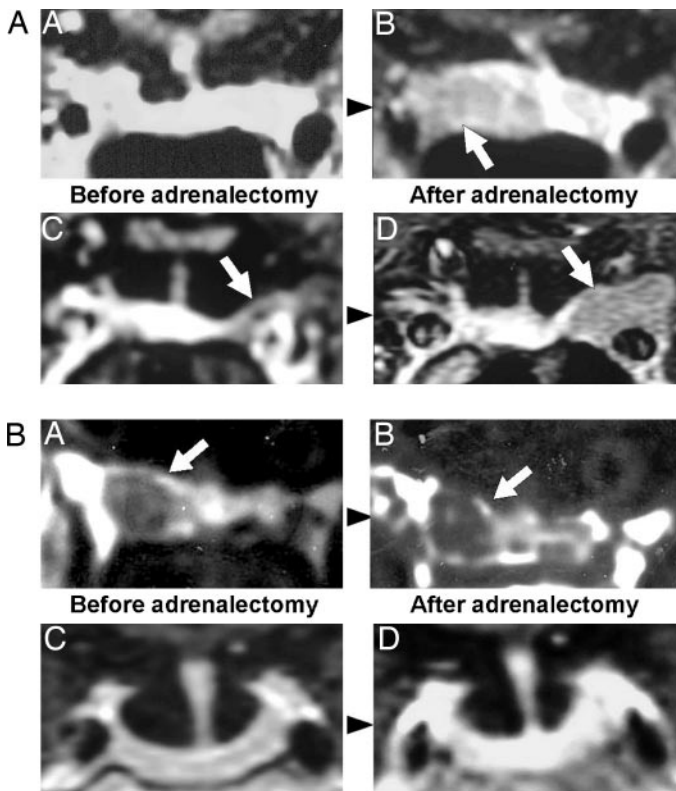
FIG. 1. Pituitary MRI of patients with and without corticotroph tumor progression. A, Corticotroph tumor progression was defined as the occurrence of an adenoma (B) if no adenoma was visible before adrenalectomy (A) or as an increase in the size of an adenoma (D) visible before adrenalectomy (C). B, Lack of corticotroph tumor progression was defined as a lack of increase in the size of an adenoma (B) 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.

TABLE 1. Characteristics of the patients at baseline

Variable	n (%)	Median (range)
Sex		
Male	8 (15)	
Female	45 (85)	
Age at diagnosis of Cushing's disease (yr)		37.7 (18–66)
Duration of Cushing's disease before adrenalectomy (yr)		6.3 (1–26)
Adenoma documented on pituitary surgery in 28 patients undergoing pituitary surgery before adrenalectomy		
No	6 (21)	
Yes	22 (79)	
Presence of mitosis in the adenoma (n = 15)		
No	5 (33)	
Yes	10 (67)	
Presence of Ki67-immunopositive nuclei in the adenoma (n = 12)		
No	3 (25)	
Yes	9 (75)	
Urinary free cortisol before adrenalectomy (n = 49); N: 50–100 μg/24 h (137–275 nmol per 24 h)[a]		271 (26–952)
Early-morning plasma cortisol concentration at the time of adrenalectomy (n = 50); N: 100–200 ng/ml (275–550 nmol/liter)[a]		222 (93–471)
Early-morning plasma ACTH concentration at the time of adrenalectomy (n = 50); N: 0–60 pg/ml (0–13 pmol/liter)[a]		86 (13–1340)
Plasma ACTH concentration after o,p'DDD-induced cortisol deprivation (n = 20); N: 0–60 pg/ml (0–13 pmol/liter)		203 (23–742)
Pituitary MRI at adrenalectomy		
No adenoma	46 (87)	
Adenoma	7 (13)	
Residual cortisol secretion after adrenalectomy (n = 50); N: 100–200 ng/ml (275–550 nmol/liter)		0 (0–51)
Plasma ACTH concentration in the year following adrenalectomy; N: 0–60 pg/ml (0–13 pmol/liter)		424 (41–3840)

[a] Mean value during the 6 months before adrenalectomy is given. Twenty-seven patients were on o,p'DDD treatment.

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

	ACTH in the year following ADX N: 0-60 pg/ml (0-13 pmol/l)	Cortisol in the year following ADX N: 100-200ng/ml (275-550 nmol/l)	Corticotroph tumor progression after adrenalectomy[1]	Major clinical outcome	Specific treatments[2]
Corticotroph tumor progression	1327	0			-
	424	16			TSS(*)
	303	0			TSS(*)
	1506	0			TSS(*), RX(#)
	1499	38			TSS(*)
	1551	0			RX(#)
	371	15			-
	2051	0			TSS(*), RX(#)
	3840	14		Adenoma necrosis	TSS(*)
	1604	0			-
	152	0			-
	1671	8			TSS(*)
	3104	0			TSS(*)
	1410	0			-
	1222	27			TSS(*)
	495	0			-
	-	0			-
	133	6			-
	193	16		Unrelated death	-
	385	48		Unrelated death	-
	2138	6			-
NO corticotroph tumor progression	426	0			-
	872	0			-
	176	13			-
	697	2			-
	831	0			-
	375	0			-
	391	16			-
	289	0			-
	3536	0			-
	430	9			-
	42	49			-
	631	0			-
	1877	0			-
	78	0			-
	1230	0			-
	41	16			-
	54	4			-
	-	0			-
	100	12			-
	279	30			-
	262	17			-
	349	12			-
	959	0			-
	161	0			-
	369	0			-
	46	0			-
	208	0			-
	102	0			-
	400	12			-
	921	51			-
	275	0			-
	738	26			-

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

[1] 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.

[2] Specific treatments: the time when TSS was performed is figured by the *asterisk* (*) symbol in the corticotroph tumor progression after adrenalectomy column and radiotherapy by the (#) symbol.
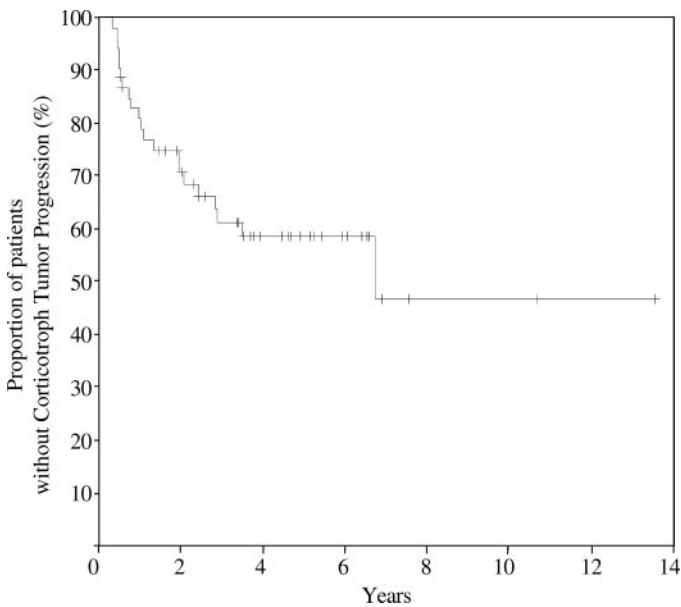
FIG. 2. Corticotroph tumor progression-free survival after adrenal-ectomy. The proportion of patients without corticotroph tumor progression during the follow-up is presented, according to the Kaplan-Meier method.

renalectomy (Table 2). Corresponding early-morning ACTH concentrations were checked for their association to corticotroph tumor progression. To identify the best way to interpret 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 concomitant to the second of consecutive MRIs. The absolute ACTH variation between consecutive MRIs gave the strongest 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, $P = 0.001$).
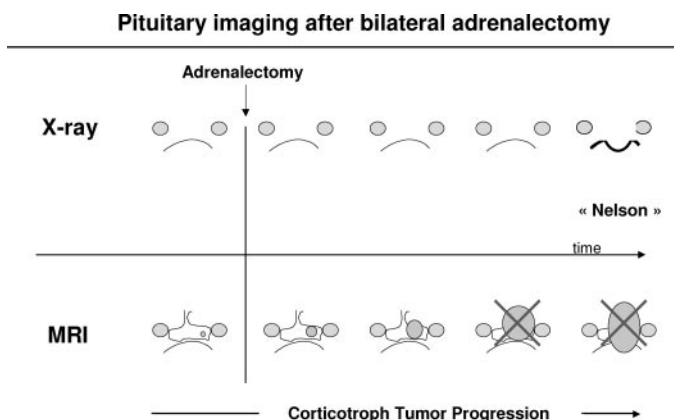

FIG. 3. Comparison of a modern approach involving corticotroph tumor progression assessment and the original concept of NS. MRI can detect early corticotroph tumor progression (*lower panel*) before the occurrence of NS, which is detected much later, by sellar floor deformation on x-ray (*upper panel*).

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 concentration. This evaluation is based on robust, modern imaging, by pituitary MRI, and the independent assessment of corticotroph tumor progression and variations in ACTH concentration. 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 absolute proof of corticotroph adenoma, *i.e.* the pathological documentation of a corticotroph adenoma, is provided for only 26 patients (18 before adrenalectomy and eight after adrenalectomy), 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 adrenalectomy, 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 corticotroph tumor progression who underwent chest computed tomography scans. Finally, for 12 patients with corticotroph tumor progression but not operated during the follow-up period, an expanding process other than the corticotroph adenoma cannot be ruled out with certainty. However, 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 sensitivity of MRI than of sellar x-rays and computed tomography 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 sensitivity 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 progression can begin later, a lifelong close follow-up with repeated pituitary MRIs should probably be recommended.

We found that a shorter duration of Cushing's disease before adrenalectomy and a high plasma ACTH concentration in the year after adrenalectomy were independent pre-

TABLE 3. Factors predictive of corticotroph tumor progression

Variable	Unadjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI
Sex				
Male	1			
Female	0.565	0.206–1.549		
Age at diagnosis of Cushing's disease (yr)	0.994	0.963–1.026		
Duration of Cushing's disease before adrenalectomy (yr)	0.874[a]	0.768–0.995	0.884[a]	0.787–0.994
Adenoma documented on pituitary surgery before adrenalectomy (n = 28)				
No	1			
Yes	1.458	0.175–12.132		
Presence of mitosis in the adenoma (n = 15)				
No	1			
Yes	43.835	0.003–718753		
Presence of Ki67-immunopositive nuclei in the adenoma (n = 12)				
No	1			
Yes	35.272	0.001–1266717		
Plasma ACTH concentration after o,p'DDD-induced cortisol deprivation (n = 20) (per pg/ml, 0.22 pmol/liter)	1.003	1.000–1.006		
Pituitary MRI on adrenalectomy				
No adenoma	1			
Adenoma	5.397[b]	2.117–13.757		
Residual plasma cortisol concentration in the year following adrenalectomy (n = 53)	0.996	0.965–1.027		
Plasma ACTH concentration in the first year after adrenalectomy (per 100 pg/ml, 22 pmol/liter)	1.057[b]	1.018–1.098	1.069[b]	1.026–1.113

[a] $P < 0.05$.
[b] $P < 0.005$.

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 shot-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 levels of secretion and the tendency toward tumor growth remains unclear.

Increase in ACTH concentration on long-term o,p'DDD-induced cortisol deprivation tended to be predictive of corticotroph tumor progression, although this relationship was not statistically significant. Indeed, o,p'DDD may be seen as the chemical equivalent of adrenalectomy. It causes an increase in ACTH concentration similar to that observed after adrenalectomy, but of a smaller amplitude, due to milder cortisol deprivation. Even if patients were selected on the basis of efficient cortisol deprivation under o,p'DDD (over 50% urinary cortisol decrease), the intensity of adrenal blockade varies. This may contribute to lower the significance of ACTH measured in these conditions for the prediction of corticotroph tumor progression. Because only a small number of patients could be tested in our study, the predictive value of ACTH concentration on o,p'DDD needs to be confirmed. This factor would then be the sole predictive factor before adrenalectomy.

Other factors, such as young age (21) and residual cortisol secretion (16, 26), previously described as predictive of NS,

were not found to be predictive of corticotroph tumor progression.

Neither the presence of mitoses nor a high percentage of Ki67-immunopositive nuclei in the adenoma was predictive of corticotroph tumor progression. Other histological parameters were studied (number of capillaries, presence of arteriolar vessels, presence of fibrosis, ratio of GH to ACTH cells in the adjacent pituitary gland), but none of these factors was predictive of corticotroph tumor progression (data not shown). This lack of significance may be due to the small number of patients studied.

After adrenalectomy, repeated MRIs are mandatory for the corticotroph tumor progression follow-up. Our aim was to identify in which way early-morning ACTH concentration could also contribute to this follow-up. Of four simple models we tested, the absolute ACTH variation between two consecutive MRIs gave the strongest association to corticotroph tumor progression in the corresponding period. This parameter should be investigated further as a potential cheap, easy-to-calculate marker of corticotroph tumor progression. It may thus improve the patient's security if performed more frequently than MRI: any important ACTH variation would prompt a rapid MRI scan.

It remains unclear whether adrenalectomy accelerates corticotroph tumor growth (39), and this study provides no definitive answer. We would need to compare corticotroph tumor progression after adrenalectomy with corticotroph tumor progression in patients with untreated hypercortisolism.

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'DDD-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.

References

1. **Nelson DH, Meakin JW, Dealy Jr JB, Matson DD, Emerson Jr K, Thorn GW** 1958 ACTH-producing tumor of the pituitary gland. N Engl J Med 259:161–164
2. **Salassa RM, Kearns TP, Kernohan JW, Sprague RG, Maccarty CS** 1959 Pituitary tumors in patients with Cushing's syndrome. J Clin Endocrinol Metab 19:1523–1539
3. **Montgomery DA, Welbourn RB, McCaughey WT, Gleadhill CA** 1959 Pituitary tumours manifested after adrenalectomy for Cushing's syndrome. Lancet 2:707–710
4. **Glenn F, Karl RC, Horwith M** 1958 The surgical treatment of Cushing's syndrome. Ann Surg 148:365–374
5. **Rees JR, Zilva JF** 1959 Diabetes insipidus complicating total adrenalectomy. J Clin Pathol 12:530–534
6. **Nelson DH, Meakin JW, Thorn GW** 1960 ACTH-producing pituitary tumors following adrenalectomy for Cushing's syndrome. Ann Intern Med 52:560–569
7. **Nagesser SK, van Seters AP, Kievit J, Hermans J, Krans HM, van de Velde CJ** 2000 Long-term results of total adrenalectomy for Cushing's disease. World J Surg 24:108–113
8. **Ernest I, Ekman H** 1972 Adrenalectomy in Cushing's disease. A long-term follow-up. Acta Endocrinol Suppl (Copenh) 160:3–41
9. **Moore TJ, Dluhy RG, Williams GH, Cain JP** 1976 Nelson's syndrome: frequency, prognosis, and effect of prior pituitary irradiation. Ann Intern Med 85:731–734
10. **Hopwood NJ, Kenny FM** 1977 Incidence of Nelson's syndrome after adrenalectomy for Cushing's disease in children: results of a nationwide survey. Am J Dis Child 131:1353–1356
11. **Cohen KL, Noth RH, Pechinski T** 1978 Incidence of pituitary tumors following adrenalectomy. A long-term follow-up study of patients treated for Cushing's disease. Arch Intern Med 138:575–579
12. **Barnett AH, Livesey JH, Friday K, Donald RA, Espiner EA** 1983 Comparison of preoperative and postoperative ACTH concentrations after bilateral adrenalectomy in Cushing's disease. Clin Endocrinol (Oxf) 18:301–305
13. **Kasperlik-Zaluska AA, Nielubowicz J, Wislawski J, Hartwig W, Zaluska J, Jeske W, Migdalska B** 1983 Nelson's syndrome: incidence and prognosis. Clin Endocrinol (Oxf) 19:693–698
14. **Kelly WF, MacFarlane IA, Longson D, Davies D, Sutcliffe H** 1983 Cushing's disease treated by total adrenalectomy: long-term observations of 43 patients. Q J Med 52:224–231
15. **Thomas Jr CG, Smith AT, Benson M, Griffith J** 1984 Nelson's syndrome after Cushing's disease in childhood: a continuing problem. Surgery 96:1067–1077
16. **Manolas KJ, Farmer HM, Wilson HK, Kennedy AL, Joplin GF, Montgomery DA, Kennedy TL, Welbourn RB** 1984 The pituitary before and after adrenalectomy for Cushing's syndrome. World J Surg 8:374–387
17. **Watson RG, van Heerden JA, Northcutt RC, Grant CS, Ilstrup DM** 1986 Results of adrenal surgery for Cushing's syndrome: 10 years' experience. World J Surg 10:531–538
18. **Grabner P, Hauer-Jensen M, Jervell J, Flatmark A** 1991 Long-term results of treatment of Cushing's disease by adrenalectomy. Eur J Surg 157:461–464
19. **McCance DR, Russell CF, Kennedy TL, Hadden DR, Kennedy L, Atkinson AB** 1993 Bilateral adrenalectomy: low mortality and morbidity in Cushing's disease. Clin Endocrinol (Oxf) 39:315–321
20. **Moreira AC, Castro M, Machado HR** 1993 Longitudinal evaluation of adrenocorticotrophin and beta-lipotrophin plasma levels following bilateral adrenalectomy in patients with Cushing's disease. Clin Endocrinol (Oxf) 39:91–96
21. **Kemink L, Pieters G, Hermus A, Smals A, Kloppenborg P** 1994 Patient's age is a simple predictive factor for the development of Nelson's syndrome after total adrenalectomy for Cushing's disease. J Clin Endocrinol Metab 79:887–889
22. **Jenkins PJ, Trainer PJ, Plowman PN, Shand WS, Grossman AB, Wass JA, Besser GM** 1995 The long-term outcome after adrenalectomy and prophylactic pituitary radiotherapy in adrenocorticotropin-dependent Cushing's syndrome. J Clin Endocrinol Metab 80:165–171
23. **Chapuis Y, Pitre J, Conti F, Abboud B, Pras-Jude N, Luton JP** 1996 Role and operative risk of bilateral adrenalectomy in hypercortisolism. World J Surg 20:775–779; discussion 779–780
24. **Imai T, Funahashi H, Tanaka Y, Tobinaga J, Wada M, Morita-Matsuyama T, Ohiso Y, Takagi H** 1996 Adrenalectomy for treatment of Cushing syndrome: results in 122 patients and long-term follow-up studies. World J Surg 20:781–786; discussion 786–787
25. **Sonino N, Zielezny M, Fava GA, Fallo F, Boscaro M** 1996 Risk factors and long-term outcome in pituitary-dependent Cushing's disease. J Clin Endocrinol Metab 81:2647–2652
26. **Pereira MA, Halpern A, Salgado LR, Mendonca BB, Nery M, Liberman B, Streeten DH, Wajchenberg BL** 1998 A study of patients with Nelson's syndrome. Clin Endocrinol (Oxf) 49:533–539
27. **Aniszewski J, Sawka A, Young WJ** The Nelson-Salassa syndrome: a longterm follow-up study. Program of the 81st Annual Meeting of The Endocrine Society, San Diego, CA, 1999, p 121 (Abstract OR42-4)
28. **Baranetsky NG, Zipser RD, Goebelsmann U, Kurman RJ, March CM, Morimoto I, Stanczyk FZ** 1979 Adrenocorticotropin-dependent virilizing paraovarian tumors in Nelson's syndrome. J Clin Endocrinol Metab 49:381–386
29. **Johnson RE, Scheithauer B** 1982 Massive hyperplasia of testicular adrenal rests in a patient with Nelson's syndrome. Am J Clin Pathol 77:501–507
30. **Ntalles K, Kostoglou-Athanassiou I, Georgiou E, Ikkos D** 1996 Paratesticular tumours in a patient with Nelson's syndrome. Horm Res 45:291–294
31. **Shekarriz M, Schneider C, Sabanegh E, Kempter F, Waldherr R** 1996 Excessive testosterone production in a patient with Nelson syndrome and bilateral testicular tumors. Urol Int 56:200–203
32. **Coste J, Strauch G, Letrait M, Bertagna X** 1994 Reliability of hormonal levels for assessing the hypothalamic-pituitary-adrenocortical system in clinical pharmacology. Br J Clin Pharmacol 38:474–479
33. **Bertagna XB, Raux-Demay MC, Guilhaume B, Girard F, Luton JP** 1995 Cushing's disease. In: Melmed S, ed. The pituitary. Los Angeles: Blackwell Science; 478–545
34. **Kaplan EL, Meier P** 1958 Nonparametric estimation from incomplete observations. J Am Statist Assoc 53:457–481
35. **Cox DR** 1972 Regression models and life-tables. J R Statist Soc 34:187–220
36. **Newell-Price J, Trainer P, Besser M, Grossman A** 1998 The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. Endocr Rev 19:647–672
37. **McKelvie PA, McNeill P** 2002 Double pituitary adenomas: a series of three patients. Pathology 34:57–60
38. **Meij BP, Lopes MB, Vance ML, Thorner MO, Laws Jr ER** 2000 Double pituitary lesions in three patients with Cushing's disease. Pituitary 3:159–168
39. **Assie G, Bahurel H, Bertherat J, Kujas M, Legmann P, Bertagna X** 2004 The Nelson's syndrome. revisited. Pituitary 7:209–215
40. **Karl M, Von Wichert G, Kempter E, Katz DA, Reincke M, Monig H, Ali IU, Stratakis CA, Oldfield EH, Chrousos GP, Schulte HM** 1996 Nelson's syndrome associated with a somatic frame shift mutation in the glucocorticoid receptor gene. J Clin Endocrinol Metab 81:124–129
41. **van der Hoek J, Lamberts SW, Hofland LJ** 2004 The role of somatostatin analogs in Cushing's disease. Pituitary 7:257–264
42. **Arnaldi G, Angeli A, Atkinson AB, Bertagna X, Cavagnini F, Chrousos GP, Fava GA, Findling JW, Gaillard RC, Grossman AB, Kola B, Lacroix A, Mancini T, Mantero F, Newell-Price J, Nieman LK, Sonino N, Vance ML, Giustina A, Boscaro M** 2003 Diagnosis and complications of Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab 88:5593–5602
43. **Dahia PL, Grossman AB** 1999 The molecular pathogenesis of corticotroph tumors. Endocr Rev 20:136–155
44. **Melmed S** 2003 Mechanisms for pituitary tumorigenesis: the plastic pituitary. J Clin Invest 112:1603–1618