Usefulness of adrenal scintigraphy in the follow-up of adrenocortical incidentalomas: a prospective multicenter study

Short Title: Prognostic value of adrenal scintigraphy

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ABSTRACT

Objectives: Prognostic factors for progression of incidentally discovered benign adrenal cortical adenomas (AI) remain poorly known. We assessed the usefulness of $^{131}$I-6βiodomethylnorcholesterol scintigraphy (IMS) to predict the occurrence of adrenal hyperfunction or mass enlargement.

Design: 51 consecutive inpatients with unilateral AI and normal 24-h urinary free cortisol were enrolled in a multicenter observational prospective study to investigate the relationship between the scintigraphic pattern and the progression of biological abnormalities of the HPA axis or tumor size.

Results: Biochemically defined “Subclinical” Cushing’s syndrome (SCS) was found at baseline in 47% of patients. Unilateral uptake (UU) was significantly associated with SCS (p<0.05). During the follow-up (4.3 +/- 1.6 yr): 53% of patients showed unchanged hormonal evaluation, 29% displayed intermittent SCS and 18% showed definitive hormonal progression of SCS but without overt biochemical hypercortisolism. UU was associated with persistence of SCS and hormonal progression (p<0.01). In multivariate analysis, UU and impaired 1 mg dexamethasone suppression were independently associated with hormonal progression. Three patients with UU developed clinical Cushing’s syndrome despite persistently normal UFC. Tumor size increased in 10% of patients and was not associated with any scintigraphic pattern.

Conclusion: Evolution of SCS towards overt biochemical CS in patients with AI is a rare event during a 4-year follow-up. UU is predictive for the occurrence of SCS, its persistence and progression within the spectrum of SCS. Further studies aiming to establish the clinical consequences of SCS are needed to recommend IMS as a complementary evaluation in patients with AI and biochemical SCS.
INTRODUCTION

Approximately 70 percent of adrenal incidentalomas (AI) discovered in patients without extra-adrenal malignancy are benign adrenocortical adenomas (1-3). Several studies have shown that a subset of these tumors secrete a mild excess of cortisol leading to the concept of “subclinical” Cushing’s syndrome (SCS) and “subclinical” cortisol-secreting adenomas (SCSA) (2). However, SCS is a heterogeneous condition and various biochemical criteria, alone or in combination, have been employed to define it (4). From a historical perspective, adrenal scintigraphy using 19-iodocholest erol allowed recognition of this entity where there was exclusive tumor uptake (5, 6). Later on, we and other groups demonstrated a clear relationship between the secretory autonomy of the adrenal tumor and the scintigraphic pattern. Indeed, unilateral norcholesterol tumor uptake was associated with increased midnight plasma cortisol concentrations, decreased 0800 h plasma ACTH and decreased cortisol suppressibility by dexamethasone compared to bilateral scintigraphic uptake (7-10). However, due to the paucity of available data on its clinical usefulness, radiocholesterol scintigraphy was not recommended as part of the evaluation of AI by the NIH conference consensus (3).

The natural history of AI and the risk that such lesions might evolve towards overt hypercortisolism remains controversial, since only a few prospective studies have been conducted (11-14). Among these, the occurrence of overt clinical Cushing’s syndrome (CS) ranges from 0 to 12.5%, whereas the development over time of new subtle biochemical abnormalities is likely to be more frequent (11-16, 22, 30).

Identification of prognostic factors would be useful to select patients at risk for disease progression, to adapt the follow-up and/or to decide whether to proceed to surgery. Few studies have addressed this issue. Tumor size $\geq$ 3 cm at diagnosis (14, 16) and exclusive tumor radiocholesterol uptake (14) were found to be associated with the occurrence of endocrine hyperfunction. On the other hand, a recent prospective study conducted by Bernini et al (12) did not find any baseline predictor for disease progression. However, adrenal scintigraphy was not performed in this study.

The aim of the present study was to prospectively assess the long-term clinical, morphological and hormonal outcome of patients with adrenocortical incidentalomas and to determine if the uptake
pattern on radiocholesterol scintigraphy could predict the occurrence of adrenal hyperfunction or mass enlargement.

PATIENTS AND METHODS

PATIENTS

Sixty-one consecutive patients with adrenal incidentalomas were enrolled in a prospective study including four French university hospitals (Angers, Bordeaux, Caen, and Tours) from January 1996 to December 2001. To be included, patients had to fulfill the following criteria: 1- imaging characteristics suggesting benign adrenocortical adenoma at CT scan analyzed by an experienced radiologist, defined on size \( \leq 40 \) mm, low attenuation value (< 10 UH), and a washout at 10-15 min of more than 50% after iv contrast administration (17); 2- lack of specific signs of Cushing’s syndrome (CS) (muscle wasting, purple striae, skin atrophy, spontaneous ecchymosis) after careful examination by an experienced endocrinologist; 3- 24-h urinary free cortisol (UFC) excretion in the normal range, 4- normal plasma renin activity and aldosterone in supine and upright positions and normal 24-h urinary metanephrine excretion.

The study was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Basse-Normandie. Each patient included in the study gave written informed consent.

STUDY DESIGN

*Baseline and follow-up investigations*

All patients were explored as in-patients. Baseline investigations consisted in clinical examination, CT scan, adrenal scintigraphy and hormonal measurements. Biochemical HPA axis evaluation included measurements of midnight and 0800 h plasma cortisol, 0800 h plasma ACTH, cortisol after 1 mg dexamethasone suppression test (DST) and 24-h UFC.
After initial diagnosis, patients were reinvestigated at 1-yr intervals with the same clinical, radiological and hormonal investigations. In addition, twenty-three patients had a second adrenal scintigraphy at the end of their follow up.

Definition and criteria of outcome

From a hormonal perspective, patients were considered at baseline as having either “Subclinical” Cortisol-Secreting Adenoma (SCSA) or Non-secreting Adenomas (NSA). SCSA was arbitrarily defined as the presence of at least two HPA axis abnormalities including low 0800 h plasma ACTH, elevated 2400/0800 h cortisol ratio, elevated midnight plasma cortisol, with a compulsory condition of impaired serum cortisol suppression after 1 mg DST (50 nmol/l). Importantly, all patients including those classified as having SCSA displayed normal 24h UFC at baseline evaluation.

During follow-up, biochemical features were defined as persistent when found at baseline and at each follow-up evaluation. Otherwise, they were considered as intermittent. Patients were consequently categorized as having persistent SCSA, persistent NSA or intermittent SCSA.

Hormonal progression was defined as followed: 1- patients with NSA at baseline in whom at least two HPA axis abnormalities appeared and persisted during follow-up (e.g. switch from NSA to SCSA); 2- patients with SCSA at baseline in whom at least one additional HPA axis abnormality appeared and persisted over time. Overt biochemical CS was defined by the occurrence of elevated UFC (> 1.5 above the upper limit of the normal range of the assay).

Clinical progression was defined as the emergence of at least one specific sign of CS considered as obvious and persistent by the referent endocrinologist regardless of the results of hormonal evaluation.

Tumoral progression was defined on CT scan as a 1-cm or greater increase in tumor diameter.

The decision to proceed to surgery was considered at each follow-up evaluation in the absence of adequate control of diabetes or hypertension, occurrence of clinical CS, development of overt biochemical CS or significant growth of the adrenal mass.

METHODS

Biochemical testing
Hormonal measurements were performed in the reference laboratories of each participating university hospital using commercially available immunoassays kits: plasma cortisol (Coat a Count; DPC, Los Angeles, CA, USA); urinary cortisol (Cis Bio International); plasma ACTH (Brahms, Berlin, Germany). The normal range for ACTH concentrations at 0800 h was 2-14 pmol/l. The upper limit of normal for midnight cortisol concentration was set at the mean + 2 SD of values measured in 28 controls hospitalized for major obesity (116 nmol/l). The normal range for 2400 h UFC was 20-90 µg/24 h. The circadian rhythm of plasma cortisol was considered normal if the ratio between cortisol at midnight and cortisol at 0800 h was less than 50%. Normal level of suppression after 1 mg DST was a plasma cortisol level below 50 nmol/l (1.8 µg/dl).

HPA axis abnormalities were therefore defined as follows: midnight plasma cortisol concentration ≥ 116 nmol/l; 2400/0800 h percent cortisol ratio ≥ 50 %; 0800 h plasma ACTH concentration ≤ 2 pmol/l; UFC > 135 µg/24h; 0800 h plasma cortisol concentration after 1 mg dexamethasone ≥ 50 nmol/l (18-21)

**Adrenal scintigraphy**

Adrenal scintigraphy was performed in basal conditions, before or at least one week after DST, after injection of 37 MBq of $^{131}$I-6βiodomethylnorcholesterol (Norchol-131®; CIS Bio International, Gif sur Yvette, France). Lugol's solution was administered daily, 2 days prior to and throughout the week of scanning, in order to suppress thyroid accumulation of 131I. Adrenal imaging was performed using a gamma camera equipped with a high-energy, parallel-hole collimator. Posterior and anterior abdominal images (15 min/image) were obtained on day 4 to 7. The interpretation of the adrenal scintigraphy was performed qualitatively by an experienced nuclear medicine physician who was blind to the result of hormonal investigations. Two types of interpretation were defined: bilateral adrenal uptake, whether prevalent on the adrenal mass or symmetrical (group I); unilateral uptake concordant with the adrenal mass, with no visualisation of the contralateral gland (group II).

**Statistical analysis**

Results were expressed as mean ± standard deviation (SD). Comparisons were based on the Fisher exact test or Chi-square test for categorical variables as appropriate and the Student’s t-test was used to
compare continuous variables. For statistical purposes, the value corresponding to the limit of detection of assays was used for undetectable concentrations of plasma cortisol and ACTH (27 nmol/l and 1.1 pmol/l respectively). Three stepwise multiple logistic regressions were used to identify prognostic factors for determination of patients at risk of: 1) hormonal progression; 2) tumoral progression. We evaluated scintigraphic pattern (unilateral vs. bilateral uptake) as a putative prognostic factor. Additional parameters were selected and dichotomized as appropriate: obesity (BMI cutoff, 30 kg/m²), presence of arterial hypertension (blood pressure cutoff: 140/90 mmHg), presence of diabetes (glycemia cutoff: 126 mg dl/l), presence of isolated endocrine abnormalities (below or over normal range), tumor size (cut-off, 3.0 cm). All variables that were \( P < 0.25 \) by univariate analysis or known to be associated with hormonal or tumoral progression in previous research (14, 16) were entered into the logistic regression model. \( P < 0.05 \) was considered statistically significant. Data were analyzed with SAS statistical software (release 8.01; SAS Institute, Cary, NC).

RESULTS

BASELINE EVALUATION

61 patients were enrolled in the study. Ten patients dropped out before the first year of follow-up by their own decision. Data for those patients were not taken in consideration.

According to our criteria, SCSA was found in 24/51 patients (47%) and NSA in 27 patients (53%). The main characteristics of patients are summarized in Table 1.

On adrenal scintigraphy, 29/51 patients (57%) showed bilateral uptake (group I) and 22 (43%) showed unilateral uptake (group II). Since normal UFC was mandatory to participate to the study, mean UFC was similar between the 2 groups of patients. However, compared to patients with bilateral uptake, patients with unilateral uptake displayed lower 0800 h plasma ACTH concentration (2.5±1.1 vs. 4.3±2.2 pmol/l, \( p<0.01 \)), higher plasma cortisol concentration following the overnight 1 mg DST (113±86 vs. 57±50 nmol/l, \( p<0.01 \)) and larger tumor size (27±7 vs. 21±8 mm, \( p<0.01 \)). Patients in group II displayed an increased number of HPA axis abnormalities compared to group I patients (2.1±1.2 vs. 1.1±1.1 respectively; \( p<0.05 \)). Accordingly, the proportion of unilateral tumor uptake was higher in patients with SCSA than in patients with NSA (62% vs. 26%, \( p<0.05 \)).
FOLLOW UP STUDY

51 patients (28 females, 23 males; mean age 61.8 ± 8.6 years) with adrenocortical adenoma were followed during 4.3 ± 1.6 years.

Hormonal outcome

In the whole group of patients, no significant change in each biological parameter was found between baseline and the latest evaluation (Table 2). However, individual evaluation showed frequent fluctuation in the results of biochemical investigations. 35% of HPA axis abnormalities found at baseline were no longer present at the last evaluation. Among the 52 new HPA axis abnormalities that appeared in 33 patients, only 14 in 13 patients persisted at subsequent evaluations.

No case of evolution towards overt biochemical Cushing’s syndrome was observed.

Figure 1 schematizes the hormonal outcome observed. Among patients with SCSA at baseline (n=24), 14 (58%) displayed persistent SCSA, 6 (25%) showed hormonal progression and 4 (17%) patients showed intermittent SCSA.

Among patients with NSA at baseline (n=27), 13 (48%) showed persistent NSA throughout the follow-up study, 11 (41%) presented intermittent SCSA and 3 (11%) showed hormonal progression towards persistent SCSA.

Tumor size outcome

On average, no variation in mass size was found between values at baseline and at the latest evaluation (24 ± 8 mm vs. 25 ± 9 mm). Individual evaluation revealed increases in tumor size in five patients (10%) and decrease in one patient (2%). Mass enlargement occurred after 1 to 5 years of follow-up, and was never associated with radiological criteria of malignancy. One patient with an increase tumor size underwent surgery; histology revealed a hematoma inside an adrenal adenoma.

Clinical outcome

Although no patients exhibited overt biochemical CS, three patients (6%) developed clinical signs of CS within the first two years of follow-up (Table 3). One patient had four persistent abnormalities of
the HPA axis, one with SCSA at baseline evaluation developed a third persistent abnormality, and one patient with only impaired 1mg DST at baseline progressed towards SCSA. All three patients displayed unilateral radiocholesterol uptake (group II). Tumor size remained stable in each patient. All three patients underwent adrenal surgery with confirmation of benign adrenocortical adenoma. After surgery, specific signs of CS have gradually disappeared after few years and two patients (n°1 and 2) improved their blood pressure.

**Prognostic factor analysis**

The persistence of biological abnormalities of the HPA axis found at baseline evaluation tended to be more frequently observed in patients with unilateral uptake than in those with bilateral uptake (71% vs. 46% of cases, p=0.07). Hormonal progression occurred in nine patients (18%). This progression was observed within the first two years in eight patients and after four years of follow-up in one patient. Only one of these patients showed apparent adrenal mass enlargement. Among these nine patients, 7 displayed unilateral uptake at baseline. Thus, hormonal progression was more frequently observed in patients with unilateral than in bilateral radiocholesterol uptake (p < 0.05). Overall, unilateral uptake was significantly associated with persistent SCS and hormonal progression within the spectrum of SCS (p < 0.01). Using multivariate analysis, unilateral tumor uptake and impaired 1 mg DST independently predicted for hormonal progression (*Table 4*). Furthermore, no significant association between mass enlargement and scintigraphic pattern was found.

**Scintigraphic evolution**

Twenty three patients had a second IMS at the last evaluation (fourteen patients in group I and nine patients in group II). Among these patients, there was no difference in the interpretations of adrenal scintiscans between baseline and last evaluation.

**DISCUSSION**
There are still uncertainties concerning the natural history of AI. The risk that such lesions evolve towards overt hypercortisolism is minimal and less than 1% in most studies published, whereas the development over time of new subtle biochemical abnormalities is likely to be more frequent (11, 12, 16, 22, 30). Only one group reported a 12.5% estimated cumulative risk to develop overt Cushing’s syndrome after 1 year (13-15). Since the optimal duration of follow-up remains unknown (3, 12), identification of prognostic factors for hormonal progression would be helpful to select patients in whom “preventive” surgery might be indicated or in whom prolonged and careful follow-up might be required. To date, such prognostic factors to identify patients at risk of progression have not been well defined. A mass size ≥ 3 cm (14, 16) and the presence of subtle biochemical endocrine abnormalities (14) have been suggested to predict evolution toward Cushing’s syndrome but are not widely accepted (12, 13). Only one prospective study claimed that exclusive radiocholesterol uptake by the mass at baseline evaluation was associated with an increased occurrence of cortisol hypersecretion during a 4-year follow-up (14). Thus, due to the paucity of available data on its clinical usefulness and putative redundancy with the results of biochemical investigations, radiocholesterol scintigraphy was not recommended as part of the evaluation of adrenal incidentalomas by the NIH conference consensus (3).

As expected, baseline biochemical investigation showed variable patterns of cortisol secretion amongst the adrenocortical tumors of the present study. 47% of these showed 2 or more abnormal HPA axis routine tests and were considered as SCSA. In the absence of consensual definition of SCS, various biological criteria have been used across studies (1, 4, 14, 16, 22, 23). It is generally admitted that it is pertinent, from a biological perspective, to consider the diagnosis of SCS in the presence of several mild alterations of the endocrine tests used for the diagnosis of overt Cushing’s syndrome. Consequently, we defined SCS as the presence of at least two HPA axis abnormalities with a compulsory condition of impaired suppression of serum cortisol after 1 mg DST, a hallmark of abnormal steroid secretion with a high negative predictive value (3). In accordance with the recent guidelines for the diagnosis of Cushing’s syndrome, we used the 50 nmol/l cutoff to enhance the sensitivity to diagnose subtle cortisol secretory autonomy (24). Several studies, including some of ours, have shown that such a low threshold may be required to diagnose subtle cortisol secretory autonomy due to adrenal tumors in patients with type 2 diabetes or osteoporosis (25-27).
A particular condition of our study was that only patients with normal UFC at baseline were included. Subtle pathological increases in nighttime cortisol secretion may not be reflected in 24h UFC measurement (28, 29) and the unequivocal elevation of UFC (> 1.5 N) reflects an increase in daily production of cortisol that we did not consider consistent with mild hypercortisolism. We therefore arbitrarily considered that an increase in UFC at baseline was not consistent with SCS but was more likely related to previously unknown, overt, Cushing’s syndrome. In accordance with previous studies, exclusive radiocholesterol uptake by the adrenal mass in our study indicated a greater degree of functional autonomy than bilateral uptake and was significantly associated with biological SCS (7-9).

Although a number of retrospective studies with inherent methodological bias have been published (2), only a few prospective studies provide detailed evaluation of hormonal secretion throughout follow-up (12-14). Barzon et al. (13) reported hormonal progression towards overt CS in only 4 of 130 patients in 5 years of follow-up. However and in accordance with most of the prospective and retrospective studies, no evolution towards overt biochemical Cushing’s syndrome was observed in the present study (12, 16, 22, 30). This emphasizes the fact that the majority of adrenocortical incidentalomas remains hormonally and morphologically unchanged at least during a 4-year follow-up. Studies aimed at the identification of prognostic factors for evolution with adequate statistical power are therefore difficult to conduct and require a huge number of patients followed during a very long period of time. A part from progression towards overt biochemical Cushing’s syndrome, careful analysis of biochemical investigations of the HPA axis during follow-up showed variable evolutive patterns within the spectrum of mild cortisol secretory dysregulation. Indeed, 29% of patients displayed a variable number of abnormal HPA axis tests from one evaluation to another and alternately fulfilled criteria for NSA or SCSA. Thus, and as demonstrated in overt Cushing’s syndrome of various etiology (31-33), variable hormonogenesis also occurs in ‘subclinical’ Cushing’s syndrome. This concept of intermittent SCS has seldom been mentioned (12, 22) but is important to consider, since identification of an additional biochemical abnormality in the follow-up of patients with AI does not necessarily reflect a definitive progression towards overt hypercortisolism. We cannot exclude that some apparent fluctuations might be related to a lack of reproducibility of the biological tests in the range of small increases and in measuring values at the end of normal ranges (4). This is specifically of importance for putative false-positives that may misclassify patients as showing
hormonal progression. These findings emphasize the need for great caution in the analysis of follow-up investigations and in the decision to proceed with surgery because of subtle hormonal pattern changes. In order to limit the impact of inaccurate hormonal evaluation, additional subtle abnormalities of HPA axis that were noted during the course of observation had to persist at each evaluation to be interpreted as true hormonal progression. Interestingly, biochemical abnormalities of the HPA axis were only transient in more than half of patients with BU while they persisted in more than 2/3rd of patients with UU. Thus, UU was associated with permanent abnormal cortisol secretory autonomy. In our study, 18% of patients showed established hormonal progression without occurrence of overt biochemical Cushing’s syndrome. Bernini et al. (12) reported that the estimated cumulative risk of developing subclinical endocrine abnormalities over time was 57% and progressive up to 80 months. It is important to note that, unlike Bernini et al. (12), we did not consider biological abnormalities such as elevated androgen levels in women, alterations in the renin-angiotensin system or mild increases in catecholamine levels in our study. Indeed, all biochemical abnormalities that we took into account to define progression were markers of adrenal autonomy (impaired dexamethasone suppression, low 0800h plasma ACTH concentration) and cortisol secretory hyperactivity (elevated midnight cortisol, disrupted cortisol circadian rhythm and elevated 24-h UFC).

In this perspective, the main findings of our study are that exclusive radiocholesterol uptake is associated with the persistence of SCS during the follow-up and with hormonal progression. On the contrary, bilateral uptake is more frequently associated with a persistent non-secreting phenotype or intermittent SCS. Using multivariate analysis, impaired 1 mg DST and exclusive radiocholesterol uptake by the mass were significantly associated with hormonal progression. Interestingly, statistical analysis revealed that these two parameters were independent factors for hormonal progression, suggesting that their intrinsic predictive value is not redundant. One may also note that, contrary to the results of biochemical investigations, the scintigraphic pattern was very stable over time, since initial unilateral or bilateral uptake was confirmed in every case at the end of follow-up. Although IMS provides complementary information, its routine use faces to some drawbacks. Today, the radiocholesterol analog is not available worldwide, in particular in North America. The radiation exposure related to IMS is estimated to 67 mSv (34), i.e. approximately six times higher than that related to an abdominal CT scan. Finally, although IMS has been found cost-effective in the diagnostic
assessment of AI at the end of the 90s in the USA (35), the cost of the radiopharmaceutical remains relatively high in France (about 600 euros). As noted in some studies, tumor size was slightly but significantly greater in SCSA than in NSA (16, 36). In accordance with a previous study (12) but contrary to others (14, 16), tumor size was not associated with hormonal progression.

One may question the clinical relevance of subtle subclinical abnormalities of HPA axis tests and, consequently, the need to predict the evolution of an exclusively “biochemical” disease. However, a number of studies suggest that SCS might not be completely silent and could be involved in the pathogenesis of morbid entities such as obesity, diabetes and hypertension (23, 36, 37-41). Thus, identification of patients at risk to be exposed to sustained mild hypercortisolism might be of interest. In addition, one may note that 6% of patients of this series who presented with SCSA, unilateral tumoral uptake and hormonal progression during follow-up, developed specific signs of clinical Cushing’s without overt biochemical hypercortisolism. This suggests that, in susceptible individuals, sustained mild hypercortisolism may contribute to the development of classical features of overt Cushing’s syndrome (42). Interestingly, resolution of “specific” symptoms of Cushing’s syndrome such as skin bruising, proximal muscle weakness and facial plethora has been described after surgical excision of SCSA (43).

In conclusion, our study shows that mild hypercortisolism may be intermittent in almost one-third of patients with apparent SCSA and confirms that the evolution of SCSA towards overt hypercortisolism is a rare event at least in the short-term (12, 13, 16, 22, 30). We confirm the results of previous studies showing that unilateral uptake at IMS is significantly associated with secretory autonomy of adrenocortical adenomas (7-9). In addition we show that a unilateral scintigraphic uptake is associated with the persistence of SCS during follow-up and is an independent prognostic factor for hormonal progression within the spectrum of SCS. The practical usefulness of this information has to be balanced with the limitations of IMS. To date, the management of SCSA is largely empirical since there is no evidence-based demonstration of its long-term metabolic and cardiovascular consequences (37). An ideal observational prospective study aiming to correlate the IMS pattern with the long-term clinical evolution of patients with benign adrenocortical incidentalomas is unrealistic. Elsewhere, prospective and controlled studies are needed to establish the benefits of surgical excision of SCSA versus nonsurgical approach (e.g. observation associated with medical treatment of clinical
abnormalities) in patients that present with hypertension, obesity and impaired glucose tolerance. Demonstration of the superiority of surgery would provide a rationale for the use of IMS. IMS could then be performed in selected patients showing benign adrenocortical adenomas at CT scan and impaired dexamethasone suppression to assess more precisely the risk of exposure to chronic and evolutive SCS.
Acknowledgments

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REFERENCES


34 Radiation dose to patients from radiopharmaceuticals (addendum 2 to ICRP publication 53). *Ann ICRP* 1998 28 1-126.


LEGENDS

TABLE 1.
Clinical, hormonal and scintigraphic features at initial evaluation. The results are expressed as mean ± S.D. SCSA: Subclinical Cortisol Secreting Adenoma. NSA: Non-secreting Adenoma.

TABLE 2.
Hormonal parameters at initial and at latest follow-up evaluation. The results are expressed as mean ± S.D.

TABLE 3.
Details of patients who displayed clinical Cushing’s syndrome (CS).
↔, unchanged

TABLE 4.
Putative basal predictors for hormonal progression.
*: parameters included in the multivariate analysis. In this model, results were adjusted for age, sex and tumor size.
^: values of the hormonal tests at baseline

FIGURE 1.
Illustration of hormonal evolution during follow-up. Four evolutive profiles are depicted (see methods) (a) Persistent subclinical Cushing syndrome (SCS). (b) Hormonal progression towards SCS. (c) Intermittent SCS. (d) Persistent non-secreting adenomas (NSA).
Intermittent SCS included 15 adrenocortical incidentalomas characterized at baseline as SCSA (n=4) and NSA (n=11).
*n*: patients with hormonal progression
FIGURE 1

(a) \( n = 20 \ (14 + 6^* \) \\
(b) \( n = 3^* \) \\
(c) \( n = 15 \) \\
(d) \( n = 13 \)

Initial Evaluation  Intermediate Evaluations  Last Evaluation

Number of HPA axis abnormalities:

- SCSA
- NSA

- 2-4
- 0-1
### TABLE 1

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<td>0.35*</td>
<td>2 (0.4-8.7)</td>
<td>0.15</td>
<td>0.13 (0.01-2.3)</td>
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<tr>
<td>Tumor ≥ 30 mm (n=16)</td>
<td>4</td>
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<tr>
<td>Hypertension (n=33)</td>
<td>8</td>
<td>0.12*</td>
<td>5.4 (0.6-47.5)</td>
<td>NS</td>
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</tr>
<tr>
<td>No Hypertension (n=18)</td>
<td>1</td>
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<tr>
<td>Diabetes (n=8)</td>
<td>1</td>
<td>0.68</td>
<td>0.6 (0.06-5.8)</td>
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</tr>
<tr>
<td>No diabetes (n=43)</td>
<td>8</td>
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<tr>
<td>Obesity (n=17)</td>
<td>3</td>
<td>0.92</td>
<td>1 (0.2-5.1)</td>
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<tr>
<td>No Obesity (n=34)</td>
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<tr>
<td>Unilateral scintigraphic uptake (n=22)</td>
<td>7</td>
<td>0.03*</td>
<td>6.3 (1.2-34.2)</td>
<td>0.03</td>
<td>21 (1.3-345)</td>
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<tr>
<td>Bilateral scintigraphic uptake (n=29)</td>
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<tr>
<td>Elevated midnight cortisol (n=27) ^a</td>
<td>5</td>
<td>0.86</td>
<td>1.1 (0.3-4.8)</td>
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<tr>
<td>Normal midnight cortisol (n=24) ^a</td>
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<tr>
<td>Disrupted cortisol rhythm (n=8) ^a</td>
<td>1</td>
<td>0.68</td>
<td>0.6 (0.07-5.8)</td>
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<tr>
<td>Normal cortisol rhythm (n=43) ^a</td>
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<tr>
<td>Low morning ACTH (n=14) ^a</td>
<td>3</td>
<td>0.66</td>
<td>1.4 (0.3-6.6)</td>
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<tr>
<td>Normal morning ACTH (n=37) ^a</td>
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<tr>
<td>Impaired 1 mg DST (n=29) ^a</td>
<td>8</td>
<td>0.06*</td>
<td>8 (0.9-69)</td>
<td>0.03</td>
<td>46 (1.4-1500)</td>
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<tr>
<td>Normal 1 mg DST (n=22) ^a</td>
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