Acta Neurochir (Wien) (2007) 149: 471–479
DOI 10.1007/s00701-007-1133-1
Printed in The Netherlands

Acta Neurochirurgica

Clinical Article

Early post-operative ACTH and cortisol as predictors of remission in Cushing's disease

J. J. Acebes[1], **J. Martino**[1], **C. Masuet**[2], **E. Montanya**[3], and **J. Soler**[3]

[1] Department of Neurosurgery, Hospital Universitario de Bellvitge, Barcelona, Spain
[2] Department of Epidemiology, Hospital Universitario de Bellvitge, Barcelona, Spain
[3] Department of Endocrinology, Hospital Universitario de Bellvitge, Barcelona, Spain

Received December 1, 2006; accepted February 19, 2007; published online April 5, 2007

Summary

Aim. To study the value of early (24 h) post-operative ACTH and serum cortisol as predictors of remission after transsphenoidal surgery in Cushing's disease.

Methods. We prospectively studied 44 patients who underwent transsphenoidal surgery for Cushing's disease between 1997 and 2005. The mean follow-up period of patients after surgery was 49 months (19–102 months). The predictive value of clinical characteristics, pre-operative hormonal studies, radiological, surgical and histological findings, and post-operative hormonal studies were analysed. For the post-operative hormonal study plasma ACTH and serum cortisol were determined at 8.00 a.m. the day after surgery.

Results. After surgery, Cushing's disease remitted in 39 patients (89%) and persisted in 5 patients (11%). Three patients relapsed during the follow-up period. Only three study variables were predictive of persistence of Cushing's disease after surgery: the non identification of the adenoma in histology (an adenoma was found in 87% of the patients in remission, and in 20% of treatment failures, $p = 0.01$), the early post-operative plasma ACTH (patients in remission: 2 pmol/L (1.1–10.8 pmol/L), treatment failures: 8.2 pmol/L (1.1–12 pmol/L), $p = 0.019$), and the early post-operative serum cortisol (patients in remission: 128.4 nmol/L (27.6–4644 nmol/L), treatment failures: 797 nmol/L (606–1037 nmol/L), $p = 0.003$). ROC curves indicated that plasma ACTH $\leq$7.55 pmol/L distinguished patients in remission from treatment failures with 80% sensitivity and 97.4% specificity, and serum cortisol $\leq$585 nmol/L with 100% sensitivity and 90% specificity.

Conclusions. Twenty-four hours after transsesphenoidal surgery for Cushing's disease, and without glucocorticoids replacement, patients with serum cortisol concentrations higher than 585 nmol/L, and/or plasma ACTH higher than 7.55 pmol/L, and/or those in which an adenoma is not identified in the histological study, have a high risk of treatment failure.

Keywords: Cushing's disease; cortisol; ACTH; transsphenoidal surgery.

Introduction

Cushing's disease is the consequence of chronic adrenal hyperproduction of glucocorticoids due to excess secretion of hypophyseal ACTH. Prevalence of the disease is 39.1 cases per one million inhabitants, and the incidence is 2.4 cases per one million inhabitants per year. Hypercortisolism, when not treated, leads to serious complications, even death [1, 25]. Ever since Cushing described basophile adenomas in the hypophysis in 1932, better treatments have been sought for Cushing's disease [9, 27]. Transsphenoidal microsurgeries currently considered the preferred treatment for Cushing's disease [16, 34] and achieves remission of the disease in 55–85% of patients [7, 34]. The rarity of Cushing's disease has made it difficult to gather an substantial number of

patients in a single institution, thus hindering the search for reliable pre-operative, intra-operative and post-operative predictive factors for the outcome of treatment. The most common predictive factors described in the literature are: medical symptoms [37], pre-operative hormonal studies [13, 14, 21, 35], radiological findings [15, 16, 20, 21, 33, 40], surgical findings [9, 33], histopathological studies [15, 33, 37], and post-operative hormonal studies [8, 23, 28, 30, 35, 36].

The consequences of persistent hypercortisolism are potentially serious (inmunosuppression, poor wound healing, diabetes, high blood pressure (HBP), cardiac insufficiency, severe osteoporosis), and an early identification of patients at risk of treatment failure is important [10]. Cortisol and ACTH fall quickly after surgery in patients in remission, so that early post-operative cortisol and ACTH levels could be used as predictors of remission after transsphenoidal surgery. The common and recommended practice of using glucocorticoid replacement therapy during and after the surgical treatment of patients with Cushing's disease, interferes with early assessment of the pituitary-adrenal axis. Few studies have been able to assess the predictive value of early post-operative cortisol and ACTH, without glucocorticoid replacement.

In this study, we aimed to assess the predictive value for remission, of early post-operative plasma ACTH and serum cortisol concentrations, 24 h after transsesphenoidal surgery, in patients with Cushing's disease who were not given glucorticoid replacement therapy until blood samples for hormone determination had been withdrawn. Furthermore, we studied the predictive value of other variables that have been suggested to play a predictive role on the evolution of the disease after surgery, such as pre-operative identification through magnetic resonance imaging (MRI) of the adenoma, identification of the tumour during surgery, and histological characterisation of the tumour.

Materials and methods

From January 1997 to December 2005, 48 consecutive patients with Cushing's disease underwent transsphenoidal surgery at the Neurosurgery Department of Hospital Universitari Bellvitge. Three patients were excluded from the study because they had received other treatments before being treated in our hospital (partial adrenalectomy in one patient, pituitary surgery in two patients), and in one patient early post-operative ACTH and cortisol determination was not performed. Thus, a total of 44 patients were analysed. The mean follow-up period of the patients after surgery was 49 months (19–102 months). The same surgeon (JJA) performed all surgical interventions, performed in the morning, and using the transsphenoidal sublabial approach [1, 19].

The diagnosis of Cushing's disease was based on the criteria we published in 1997 [1] and that the literature acknowledges to be valid [1, 15, 23, 24, 34, 36, 39]. Serum cortisol (normal range: 155–678 nmol/L), 24 h urinary free cortisol (normal range: 86–631 nmol/day), and plasma ACTH (normal range: 2–12 pmol/L) were determined by chemiluminescent immunoassay, using a commercial Inmunolite 2000 kit. The lower limit of detection was 27.6 nmol/L for serum cortisol and 1.1 pmol/L for plasma ACTH.

Neuroradiological investigation included a pituitary MRI in all patients. T1 (simple and contrast enhanced) and T2 sequences were obtained. In 7 patients in whom MRI did not identify a pituitary tumour, bilateral petrosal sinus catheterisation was performed. Simultaneous ACTH was determined in both sinuses and in antebrachial vein before (basal) and after CRH administration (100 μg, I.V.). A central-peripheral gradient of ACTH concentration higher than 2 at baseline and/or higher than 3 after CRH stimulation was considered evidence that ACTH hypersecretion originated in the hypophysis. A right-left gradient higher than 1.4 was considered a sign of lateralisation [12, 22, 29, 31]. Immunocytochemical study of the pituitary included staining for ACTH, GH, PRL, FSH, LH and TSH.

The early post-operative hormonal assessment consisted of measurement of plasma ACTH and serum cortisol in all patients at 8:00 a.m. on the day after surgery. No glucocorticoid replacement therapy was administered during surgery or in the post-operative period until blood samples for ACTH and cortisol determination were obtained. The patients were closely monitored in an intensive care unit until the blood samples for hormone determination were obtained, and then the corticoid replacement treatment began.

The post-operative assessment after pituitary surgery included the measurement of 24-h urinary free cortisol, basal serum cortisol and basal plasma ACTH every 4–6 months. In patients with low or undetectable serum and/or urinary free cortisol, hypocortisolism was confirmed by the absent or subnormal response of serum cortisol to stimulus with ACTH (250 μg, I.V.). These patients were maintained on glucocorticoid therapy until the recovery of the adrenal-pituitary axis, indicated by the recovery of the normal response of serum cortisol to

ACTH stimulation. After the recovery on the adrenal-pituitary axis, a normal 24-h urinary free cortisol was used as criterion for sustained remission, and if urinary free cortisol levels showed a progressive increment in successive determinations or were above the normal range, a low dose (2 mg) dexamethasone suppression test was performed.

The patients were considered to be in remission if the symptoms of hypercortisolism remitted, and basal and ACTH-stimulated plasma cortisol and 24 h urinary free cortisol were within or below normal values during the first six months after surgery [35]. We considered that the disease persisted (treatment failure), when the above criteria were not met. Relapses were defined as a reappearance of the symptoms and a rise in blood cortisol and urinary free cortisol when more than six months had gone by since the operation [15, 36].

A Kolmogorov-Smirnov test was made to carry out a study of the distribution of each variable and P–P and Q–Q charts were used to confirm it. It was observed that the majority did not follow a normal distribution and given that the number of patients was small ($n = 44$) non-parametric tests were used for the comparisons. Values are expressed as median and range. A Mann–Whitney *U*-test was used to determine the relationship between the outcome variables (remission versus treatment failure) and quantitative variables. The relationship between the outcome variables and the qualitative values were determined by Fisher's exact test. A significance level of 5% ($p < 0.05$) was accepted in all of the cases. A logistic regression multivariate analysis adjusted by sex and age was used to study the variables that were statistically significant in the univariate test, which enabled us to determine the independent relationship of each variable with the outcome variable. SPSS software version 11.0 was used for the statistical analysis.

Results

The median age of the patients was 41.5 years (9–86 years), and there was a clear predominance of women (39 women and 5 men). All patients showed a clinical phenotype suggestive of hypercortisolism with a mean duration of symptoms of 17.6 months (2–60 months). After transsphenoidal surgery, clinical and biochemical remission of Cushing's disease was achieved in 39 patients (89%), and it persisted in 5 patients (11%). Three patients relapsed, mean time to relapse was 54.6 months (30–84 months). We re-operated on two of these patients, the third patient is currently being studied. Thirty-seven patients (84%) developed hypocortisolism after surgery and required glucocorticoid replacement treatment during a mean time of 25 months (2–102 months). At the end of follow up, 18 of the 36 (50%) patients in remission had a normal hypophyseal-adrenal axis function and 18 patients (50%) showed persistent hypocortisolism based on ACTH-stimulated cortisol values, and received glucocorticoid replacement therapy.

Before surgery, mean urinary free cortisol was 1195 nmol/24 h (56.9-3914 nmol/24 h), serum cortisol was 637 nmol/L (217–1605 nmol/L) and plasma ACTH was 15.6 pmol/L (5.2–78.1 pmol/L). The MRI identified an image clearly suggestive of adenoma in 37 patients (84.1%), in six patients (13.6%) indirect signs of a tumour were observed (increased size of one hemihypophysis, displacement of the hypophyseal stalk), and in one patient (2.3%) no evidence of tumour was found. In patients with MRI showing a tumour, the mean diameter was 6 mm (3–19 mm), there were 10 macroadenomas (diameter larger than 10 mm), and invasion of neighbouring structures next to the gland was observed in 4 cases (9.7%). The inferior petrosal sinus catheterism identified a gradient in the central-peripheral ACTH in

Table 1. *Characteristics of patients in remission and treatment failures*

	Remission (39 patients)	Treatment failures (5 patients)
Age (years)	41 (9–86)	61 (39–71)
Duration of symptoms before surgery (months)	17 (2–60)	28 (12–60)
Pre-operative UFC (nmol/24 h)	1191 (56.9–3914)	1867 (675–7711)
Pre-operative serum cortisol (nmol/L)	759 (217–1605)	722 (538–889)
Pre-operative plasma ACTH (pmol/L)	15.9 (5.2–78.1)	12.8 (11.6–26.4)
Adenoma identification in MRI	85%	80%
Maximum adenoma diameter by MRI (mm)	7	4
Signs of invasion in MRI	9.7%	0%
Adenoma identification during surgery	90%	80%
Adenoma identification in AP study	87%*	20%*
Post-operative early serum cortisol (nmol/L)	128.4 (27.6–4644)*	797 (606–1037)*
Post-operative early plasma ACTH (pmol/L)	2 (1.1–10.8)*	8.2 (1.1–12)*

Results are expressed as median (range). *$P < 0.05$.

all 7 patients. A right-left gradient in ACTH secretion was identified in 5 patients and no gradient was found in 2 patients. There were no statistically significant differences between patients in remission and treatment failures regarding the clinical, biochemical and preoperative hormonal and radiological studies (Table 1).

At surgery, a lesion suggestive of pituitary adenoma was identified in 37 subjects. Selective adenomectomy was performed in 35 patients and hemihypophysectomy encompassing the supposed tumour in 2 patients. In the 5 patients in which the adenoma was not identified during surgery, a hemihypophysectomy, guided by the results of previous petrosal sinus catheterism, was performed. Two patients in which no gradient was found at the sinus catheterism underwent a full hypophysectomy. There were no statistically significant differences for these parameters between patients in remission and treatment failures (Table 1). In 9 of the 44 patients (22.7%), the histological study did not identify the adenoma. In 5 (12.8%) of the 39 patients in remission and in 4 (80%) of the 5 treatment failures, no adenoma was identified in the histological study ($p = 0.01$) (Table 1).

Patients in remission had a median early post-operative plasma ACTH of 2 pmol/L (1.1–10.8 pmol/L), and treatment failures of 8.2 pmol/L (1.1–12 pmol/L) ($p = 0.019$) (Fig. 1). The ROC curve analysis established that an early plasma ACTH above 7.55 pmol/L distinguished between patients in remission and treatment failures with 80% sensitivity and 97.4% specificity. Patients in remission had a median early post-operative serum cortisol of 128.4 nmol/L (27.6–4644 nmol/L), and treatment failures of 797 nmol/L (606–1037 nmol/L) ($p = 0.003$) (Fig. 2). The ROC curve analysis established that an early serum cortisol above 585 nmol/L distinguished patients in remission and treatment failures with 100% sensitivity and 90% specificity.

Two of the patients in the remission group had very high values of early post-operative serum cortisol

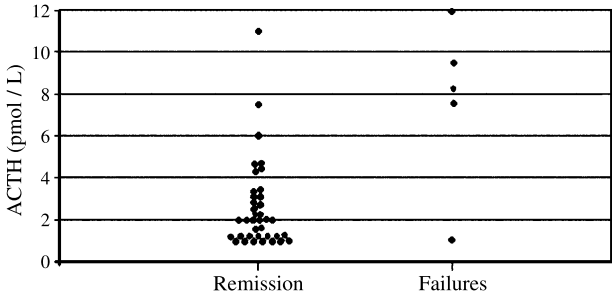

Fig. 1. Post-operative (24 h) plasma ACTH levels in patients in remission and treatment failures

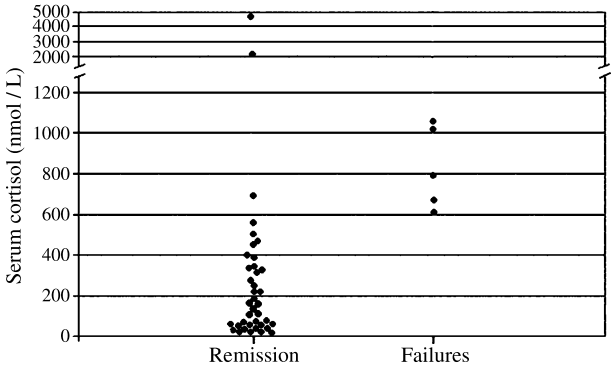

Fig. 2. Post-operative (24 h) serum cortisol levels in patients in remission and treatment failures

(patient 1: 2100 nmol/L and patient 2: 4644 nmol/L). These 2 patients achieved remission during the follow-up (77 months and 19 months, respectively) and they are currently still in remission (patient 1 has a basal serum cortisol of 320 nmol/L and UFC of 388 nmol/day, patient 2 has a basal serum cortisol of 272 nmol/L and urinary free cortisol of 187 nmol/day).

The three parameters that were statistically different between patients in remission and treatment failures in the univariate analysis (histological identification of the adenoma, early post-operative plasma ACTH and early post-operative serum cortisol) were studied using a logistic regression multivariant analysis. None of the three parameters showed a statistically significant association with the outcome variable. Early post-operative serum cortisol was the variable that came closest to statistical significance in the multivariate analysis.

The three patients who relapsed had a mean early post-operative plasma ACTH of 2.6 pmol/L (1.7–4.3 pmol/L) and a mean early post-operative serum cortisol of 86.9 nmol/L (27.6–184 nmol/L).

Discussion

The definition of remission for Cushing's disease is not uniform in the literature, and although many researchers have used a combination of clinical and biochemical criteria [9, 27, 28, 37], others have used only biochemical criteria [7, 33, 40], making it difficult to compare the results among different series. Nevertheless, the remission rate in our patients is in the upper range of the 42–87.5% remission rate reported by other groups [9, 27, 33, 38, 40].

Atkinson *et al.* [3] reviewed the long-term outcome (mean follow-up 9.6 years) in 63 patients who had pituitary surgery for Cushing's disease and identified a relapse rate of 22%. Thus, this group prefers to use the

term ''apparent remission'' instead of ''cured'' in the patients with control of Cushing's disease after transsphenoidal surgery. Other studies, have reported post-surgery relapses of up to 25% ten years after surgery [27, 33, 34, 37, 40]. In our series, with a mean follow-up of 4.1 years, three patients (7.7%) have relapsed (mean time to relapse 4.5 years), but it is probable that this number will increase in extended follow-up. The patients who relapsed had low values of early post-operative plasma ACTH (mean 2.6 pmol/L) and serum cortisol (mean 86.9 nmol/L), but the relatively short follow-up of our study doesn't allow us to reach conclusions regarding the value of early post-operative ACTH and cortisol as predictors of relapse.

There are many factors that have been previously analysed in order to determine the early identification of the patients who will suffer a therapeutic failure after transsphenoidal surgery of Cushing's disease. Most studies conclude that the pre-operative hormone variables (serum cortisol, urinary free cortisol and plasma ACTH) are of no predictive value [6, 21, 23, 35], and in our analysis these three parameters had no predictive value either. Regarding the imaging tests, the literature associates non-visualisation of the adenoma, the presence of a macroadenoma, and signs of invasion of neighbouring structures, with a worse prognosis [4–6, 8, 21, 26, 33]. In our series, however, none of these three radiological parameters was predictive in the persistence of the disease. Perhaps the small number of macroadenomas and tumours with signs of invasion on MRI can explain these discrepancies with the literature.

Finding an adenoma at surgery has been considered an indication of good prognosis in some studies. However, the type of surgery (tumourectomy, hemihypophysectomy, and others) was not considered to have a predictive value [6, 33]. We analysed adenoma identification during surgery, and type of surgery, and found that, in our experience, none of the three parameters were predictive. Histological identification of an adenoma has also been considered a good prognostic factor in several studies [6, 17, 37]. In our series, the histological study identified an adenoma in 87% of the patients in remission, but only in 20% of the treatment failures, a statistically significant difference. In our experience, this confirms that identifying an adenoma in histology is associated with better post-operative prognosis.

In Cushing's disease, after the resection of the adenoma, there is a rapid decline in blood ACTH and cortisol due to the inhibited state of the normal corticotrophin cells [9, 28, 34, 40]. However, the predictive value of immediate post-operative serum cortisol and particularly of plasma ACTH, has not been sufficiently studied. Because of the risk of acute adrenal insufficiency after adenomectomy, it is common practice to administer high doses of glucocorticoids during Cushing's disease surgery and in the post-operative period. However, this treatment can inhibit the secretion of ACTH and cortisol, making the interpretation of the early post-operative hormone studies very difficult [18, 34, 35]. The report by Simmons *et al.* [35] was, to our knowledge, the first relevant study to analyse post-operative cortisol dynamics in patients without administration of exogenous steroids. In our study, glucocorticoid treatment was withheld for 24 h until post-operative hormone measurements were performed in order to reduce the time that patients were at risk to develop adrenal insufficiency. We did not encounter features of an adrenal crisis in any patient. Because of the careful monitoring of these patients and the brief duration without glucocorticoids, we, like others, believe this is a safe practice [35].

Rollin *et al.* [34] analysed blood cortisol concentrations 6 h, 12 h and 10–12 days after hypophyseal surgery for Cushing's disease in a series of 41 patients. They concluded that the cortisol levels required several days to reach very low or undetectable levels. They, therefore, considered that serum cortisol levels 10–12 days after surgery was the best parameter to distinguish between patients in remission and treatment failures. In their study, a serum cortisol value of 207 nmol/L 10–12 days after hypophyseal surgery distinguished between patients in remission and treatment failures with 100% sensitivity and specificity. In our study, we found that 24 h after surgery, serum cortisol was already significantly different in remission and failure groups. Even at this early stage after surgery a serum cortisol value of 585 nmol/L distinguished patients in remission and treatment failures with 100% sensitivity and 90% specificity. The negative predictive value is 100%. This means that all patients with an early post-operative serum cortisol below 585 nmol/L will achieve remission. A sensitivity of 100%, guarantees that, in our series, all of the treatment failures have an early post-operative serum cortisol above 585 nmol/L. However, a specificity of 90%, reduces the positive predictive value to 62.5%, and therefore, no therapeutic decisions can be made in the group of patients with an early post-operative serum cortisol above 585 nmol/L (almost 40% will be in remission). A closer follow-up of these patients is recommended, because they are at higher risk of treatment failure.

Several other studies have shown that post-operative serum cortisol may require several days to reach very low or undetectable levels, and that measurable post-operative serum cortisol values are not always linked to failure, and can be associated with long-term remission [3, 6, 13, 17, 20, 34, 35]. In our study, 27 patients in the remission group had measurable post-operative serum cortisol levels at 8:00 am the day after surgery, and nineteen of the patients in the remission group (49%) had cortisol values in normal range (155–678 nmol/L). These data are similar to those reported by Simmons *et al.* [35] who showed that 9 of the 21 patients in their remission group (43%) had a serum cortisol above 138 nmol/L at 12:00 am the day after surgery, and by Rollin *et al.* [34] who reported that 24 h after surgery, 6 of the 21 patients in their remission group (29%) had a serum cortisol above 138 nmol/L.

Two of the patients in the remission group had very high values of early post-operative serum cortisol. These 2 patients achieved clinical and biochemical remission and are currently still in remission. A careful review of the medical records excluded inadvertent glucocorticoid administration during surgery or in the post-operative period before cortisol and ACTH determination. Although the length of follow-up of one of these patients is already substantial (77 months), a longer follow-up of both patients is still needed to determine the prognostic value of the high cortisol values found in the immediate post-operative evaluation.

The predictive value of post-operative ACTH has not been studied as extensively as that of cortisol [11, 16, 32]. In a series of 7 patients with Cushing's disease who were cured after surgery, Czirjak *et al.* [11] determined ACTH concentrations 2 h after surgery and the morning following surgery. A significant decline in ACTH concentrations 2 h after surgery was observed (6 out of 7 patients), and the decline was more significant the morning after surgery. Graham *et al.* [16] compared ACTH concentrations before surgery and one hour following tumoural extraction in a group of 18 patients. They discovered that in the group in remission ($n = 11$) the mean maximum decline of ACTH concentrations was 54%, whereas in the group of patients who remained uncured ($n = 7$) the mean maximum decline was 26%. In our series, the early post-operative ACTH concentration was significantly lower in the group of patients in remission than in treatment failures. Moreover, an early post-operative ACTH value of 7.55 pmol/L enabled us to distinguish patients in remission and treatment failures with 80% sensitivity and 97.4% specificity. Due to the high specificity, the positive predictive value is 80%, indicating that a patient with an immediate post-operative ACTH concentration higher than 7.55 pmol/L has an 80% probability of treatment failure.

In the multivariate analysis, we sought to identify the factors associated to the remission of Cushing's disease independently of the remaining variables. However, we were not able to identify any variable that, by itself, could be predictive after surgery. Due to the fact that post-operative cortisol was the variable that came closest to statistical significance in the multivariate analysis, we wonder whether it could be the only independent factor predicting the remission of Cushing's disease in early post-operative period after transsesphenoidal adenomecty.

Conclusions

Twenty-four hours after transsesphenoidal surgery for Cushing's disease, and without glucocorticoid replacement, patients with a serum cortisol concentration higher than 585 nmol/L, and/or plasma ACTH higher than 7.55 pmol/L, and/or those in which an adenoma is not identified in the histological study have a high risk of treatment failure. These patients would benefit from a closer follow-up and early treatment if treatment failure is confirmed.

Acknowledgements

We thank the endocrinology departments of the hospitals listed below for referring patients to our departments for surgical treatment: Hospital Universitari Josep Trueta (Girona), Hospital Universitari Arnau de Vilanova (Lleida), Hospital Universitari Joan XXIII and Sant Joan de Reus (Tarragona), Hospital Universitari San Joan (Alacant), Hospital de La Inmaculada de Huercal Overa (Almería), Hospital Nostra Senyora del Mar (Barcelona).

References

1. Acebes JJ, Cabiol J, Lopez L, Gabarros A, Muntanya E, Soler J (2001) Cushing's disease in the 90s: a review. Neurocirugia 12: 86–103
2. 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
3. Atkinson AB, Kennedy A, Wiggam MI, McCance DR, Sheridan B (2005) Long-term remission rates after pituitary surgery for Cushing's disease: the need for long-term surveillance. Clin Endocrinol 63: 549–559
4. Barrou Z, Abecassis JP, Guilhaume B, Thomopoulos P, Bertagna X, Derome P, Bonnin A, Luton JP (1997) Magnetic resonance imaging in Cushing disease. Prediction of surgical results. Presse Med 26: 7–11
5. Blevins LS Jr, Christy JH, Khajavi M, Tindall GT (1998) Outcomes of therapy for Cushing's disease due to adrenocorticotropin-secreting pituitary macroadenomas. J Clin Endocrinol Metab 83: 63–67

6. Bochicchio D, Losa M, Buchfelder M (1995) Factors influencing the immediate and late outcome of Cushing's disease treated by transsphenoidal surgery: a retrospective study by the European Cushing's disease survey group. J Clin Endocrinol Metab 80: 3114–3120
7. Burke CW, Adams CB, Esiri MM, Morris C, Bevan JS (1990) Transsphenoidal surgery for Cushing's disease: does what is removed determine the endocrine outcome? Clin Endocrinol (Oxf) 33: 525–537
8. Cannavo S, Almoto B, Dall'Asta C, Corsello S, Lovicu RM, De ME, Trimarchi F, Ambrosi B (2003) Long-term results of treatment in patients with ACTH-secreting pituitary macroadenomas. Eur J Endocrinol 149: 195–200
9. Chee GH, Mathias DB, James RA, Kendall-Taylor P (2001) Transsphenoidal pituitary surgery in Cushing's disease: can we predict outcome? Clin Endocrinol (Oxf) 54: 617–626
10. Chen JC, Amar AP, Choi S, Singer P, Couldwell WT, Weiss MH (2003) Transsphenoidal microsurgical treatment of Cushing disease: post-operative assessment of surgical efficacy by application of an overnight low-dose dexamethasone suppression test. J Neurosurg 98: 967–973
11. Czirjak S, Bezzegh A, Gal A, Racz K (2002) Intra- and postoperative plasma ACTH concentrations in patients with Cushing's disease cured by transsphenoidal pituitary surgery. Acta Neurochir (Wien) 144: 971–977
12. Doppman JL, Frank JA, Dwyer AJ (1988) Gadolinium DTPA enhanced MR imaging of ACTH-secreting microadenomas of pituitary gland. J Comp Assist Tomogr 12: 728–735
13. Estrada J, Garcia-Uria J, Lamas C, Alfaro J, Lucas T, Diez S, Salto L, Barcelo B (2001) The complete normalization of the adrenocortical function as the criterion of cure after transsphenoidal surgery for Cushing's disease. J Clin Endocrinol Metab 86: 5695–5399
14. Etxabe J, Vazquez JA (1994) Morbidity and mortality in Cushing's disease: an epidemiological approach. Clin Endocrinol (Oxf) 40: 479–484
15. Gonzálvez JD, Gomez JM, Montanya E, Carrera MJ, Villabona C, Acebes JJ, Soler J (1997) Evaluación de los factores pronósticos en la curación de la enfermedad de Cushing intervenida por via septotransesfenoidal. An Med Intern 14: 337–340
16. Graham KE, Samuels MH, Raff H, Barnwell SL, Cook DM (1997) Intraoperative adrenocorticotropin levels during transsphenoidal surgery for Cushing's disease do not predict cure. J Clin Endocrinol Metab 82: 1776–1779
17. Guilhaume B, Bertagna X, Thomsen M, Bricaire C, Vila-Porcile E, Olivier L, Racadot J, Derome P, Laudat MH, Girard F (1988) Transsphenoidal pituitary surgery for the treatment of Cushing's disease: results in 64 patients and long term follow-up studies. J Clin Endocrinol Metab 66: 1056–1064
18. Hamrahian AH, El-Manllawany NK, Arafan BA (1999) Evaluation and management of pituitary-adrenal function after pituitary surgery. Endocrinologist 9: 16–24
19. Hardy J (1979) The transsphenoidal surgical approach to the pituitary. Hosp Pract 14: 81–89
20. Invitti C, Giraldi FP, de MM, Cavagnini F (1999) Diagnosis and management of Cushing's syndrome: results of an Italian multicentre study. Study Group of the Italian Society of Endocrinology on the Pathophysiology of the Hypothalamic-Pituitary-Adrenal Axis. J Clin Endocrinol Metab 84: 440–448
21. Kristof RA, Schramm J, Redel L, Neuloh G, Wichers M, Klingmuller D (2002) Endocrinological outcome following first time transsphenoidal surgery for GH-, ACTH-, and PRL-secreting pituitary adenomas. Acta Neurochir (Wien) 144: 555–561
22. Landolt AM, Schubiger O, Maurer R, Girard J (1994) The value of inferior petrosal sinus sampling in diagnosis and treatment of Cushing's disease. Clin Endocrinol (Oxf) 40: 485–492
23. Leinung MC, Kane LA, Scheithauer BW, Carpenter PC, Laws ER Jr, Zimmerman D (1995) Long term follow-up of transsphenoidal surgery for the treatment of Cushing's disease in childhood. J Clin Endocrinol Metab 80: 2475–2479
24. Losa M, Mortini P, Dylgjeri S, Barzaghi R, Franzin A, Mandelli C, Giovanelli M (2001) Desmopressin stimulation test before and after pituitary surgery in patients with Cushing's disease. Clin Endocrinol (Oxf) 55: 61–68
25. Ludecke DK (1991) Transnasal microsurgery of Cushing's disease 1990. Overview including personal experiences with 256 patients. Pathol Res Pract 187: 608–612
26. Mampalam TJ, Tyrrell JB, Wilson CB (1988) Transsphenoidal microsurgery for Cushing disease. A report of 216 cases. Ann Intern Med 109: 487–493
27. McCance DR, Besser M, Atkinson AB (1996) Assessment of cure after transsphenoidal surgery for Cushing's disease. Clin Endocrinol (Oxf) 44: 1–6
28. McCance DR, Gordon DS, Fannin TF, Hadden DR, Kennedy L, Sheridan B, Atkinson AB (1993) Assessment of endocrine function after transsphenoidal surgery for Cushing's disease. Clin Endocrinol (Oxf) 38: 79–86
29. Miller DL, Doppman JL (1991) Petrosal sinus sampling: technique and rationale. Radiology 178: 37–47
30. Newell-Price J (2002) Transsphenoidal surgery for Cushing's disease: defining cure and following outcome. Clin Endocrinol (Oxf) 56: 19–21
31. Oldfield EH, Doppman JL (1998) Petrosal versus cavernous sinus sampling. J Neurosurg 89: 890–893
32. Raff H, Shaker JL, Seifert PE, Werner PH, Hazelrigg SR, Findling JW (1995) Intraoperative measurement of adrenocorticotropin (ACTH) during removal of ACTH-secreting bronchial carcinoid tumors. J Clin Endocrinol Metab 80: 1036–1039
33. Rees DA, Hanna FW, Davies JS, Mills RG, Vafidis J, Scanlon MF (2002) Long-term follow-up results of transsphenoidal surgery for Cushing's disease in a single centre using strict criteria for remission. Clin Endocrinol (Oxf) 56: 541–551
34. Rollin GA, Ferreira NP, Junges M, Gross JL, Czepielewski MA (2004) Dynamics of serum cortisol levels after transsphenoidal surgery in a cohort of patients with Cushing's disease. J Clin Endocrinol Metab 89: 1131–1139
35. Simmons NE, Alden TD, Thorner MO, Laws ER (2001) Serum cortisol response to transsphenoidal surgery for Cushing disease. J Neurosurg 95: 1–8
36. Soler J (1992) Factores pronósticos en la enfermedad de Cushing. Endocrinol 39: 206–207
37. 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
38. Trainer PJ, Lawrie HS, Verhelst J, Howlett TA, Lowe DG, Grossman AB, Savage MO, Afshar F, Besser GM (1993) Transsphenoidal resection in Cushing's disease: undetectable serum cortisol as the definition of successful treatment. Clin Endocrinol (Oxf) 38: 73–78
39. van Aken MO, Singh R, van den Berge JH, Tanghe HL, Pieterman H, de Herder WW (1996) Cushing's disease: successful surgery through improved pre-operative tumor localization. Ned Tijdschr Geneeskd 140: 1455–1459
40. Yap LB, Turner HE, Adams CB, Wass JA (2002) Undetectable postoperative cortisol does not always predict long-term remission in Cushing's disease: a single centre audit. Clin Endocrinol (Oxf) 56: 25–31

Comments

In this paper, the authors performed surgery early in the morning, and then early the following morning after surgery and measured

basal ACTH and cortisol levels in their patients. As has been noted by others who have studied this systematically, the cortisol levels tend to fall within the first 24–36 hours to subnormal levels in patients who are destined to have an excellent and long lasting remission. It is true that some patients have cortisol levels that fall at a slower rate then others, undoubtedly dependent upon the activity of the normal corticotrophs in the normal pituitary gland which may not be totally suppressed, particularly in patients who have mild disease. For that reason, it is our protocol to measure the serum cortisol every 6 hours following surgery for removal of an ACTH secreting adenoma associated with Cushing's disease. We have reported these findings and they are certainly similar to those reported by Acebes and Colleagues.

Obviously, it is important to continue to follow these patients, as late recurrences develop; and in our series the 10 year recurrence rate is over 12%, and the 20 year recurrence rate, even in patients who have met all of the criteria for early remission is over 20%. This simply emphasizes the difficulties of dealing with patients with Cushing's disease and the need for accurate diagnostic and prognostic information as provided in this excellent paper.

Edward R. Laws
Charlottesville, VA

Cushing's disease remains a complex challenge for clinical Neurosurgeons and Endocrinologists. Long-term remission rates following transsphenoidal pituitary adenectomy vary from 50 to 80% [1], and there is considerable interest in identifying factors that will predict subsequent clinical outcome as these will help decisions on the need for early further treatment. In this issue, Acebes and colleagues report the value of early measurement of ACTH and cortisol in prediction of subsequent relapse or remission after transsphenoidal surgery for Cushing's disease. Forty four patients were operated on, and followed for a minimum of nineteen months. The apparent remission rate was higher than reported in other series (89%), and only five patients had persistent disease. However, three of the patients in apparent remission did relapse during the follow-up period (in other words, had recurrence of symptoms and biochemical features of Cushing's disease after apparent cure more than six months after the initial operation). Of the variables that apparently predicted persistence of Cushing's disease, the inability to identify an adenoma at the time of surgery was significantly associated with failure to achieve remission. Of the biochemical data, plasma ACTH and cortisol (both measured within 24 hours of surgery) apparently predicted outcome. In particular, after statistical evaluation using ROC analysis, a serum cortisol of less than 585 nmol/L distinguished patients who had achieved remission from those who failed to do so with 100% sensitivity and 90% specificity. Do these new data add to our understanding and help in the management of Cushing's disease?

Firstly, it is important to note that the series represents the experience of a single surgeon. Diagnosis was made on conventional grounds although in only seven patients was inferior petrosal sinus sampling performed and in the rest of the subjects there was clear evidence of a tumour on MR imaging. Post-operative pathology was available in all subjects. No patient was given glucocorticoid replacement until post-operative assessment was performed at 0800 on the day after surgery (in other words, slightly less than 24 hours after the operation itself).

If there was elevation of urinary cortisol a low dose Dexamethasone suppression test was performed to look for evidence of relapse. However, no formal Dexamethasone suppression or measurement of cortisol diurnal rhythm was performed on a routine basis at other times during follow-up.

There are a number of potential problems with the interpretation of the data presented. Inspection of figures 1 and 2 show ACTH and cortisol levels, respectively, following treatment. It will be noted that in both the remission and failure groups there is a wide range of values. For cortisol, two patients who had apparently achieved remission had extraordinarily high levels (greater than 2000 nmol/L), and a substantial number of patients in apparent remission had cortisol levels that were easily measurable (greater than 200 nmol/L) at this time. In contrast, in patients who failed treatment, the cortisol levels were all greater than 585 nmol/L but there is substantial overlap between the groups. Thus, although the data are statistically of interest it remains unclear what practical message can be taken from this study. In particular, two main questions arise.

How do these data compare with other studies of post-operative assessment following treatment of Cushing's disease? In a recent paper, Atkinson and colleagues present data from Northern Ireland on long-term remission rates after pituitary surgery for Cushing's disease. In this study, they report an overall remission rate of 56% after protracted follow-up (median duration 115 months; range 1 to 21 years). In this study, post-operative assessment was carried out using a low dose Dexamethasone suppression test. Of the subjects who showed a late relapse (despite an apparent initial remission) three (of ten) had a baseline cortisol level approximately five days after surgery of less than 50 nmol/L, and all ten had baseline cortisols less than the cut-off described in the current paper of 585 nmol/L. In contrast, of the patients who apparently remained in remission, fourteen of thirty five subjects showed a baseline cortisol of greater than 50 nmol/L and two failed a conventional low dose Dexamethasone suppression test. In only one of the subjects, however, was baseline cortisol greater than 585 nmol/L. This study, therefore, suggests that early apparent remission is not, necessarily, associated with a long-term cure (Acebes and colleagues are also careful to point out that remission does not equate to cure).

The study of Atkinson also confirms the finding of Acebes that some patients in whom early post-operative cortisol measurements are elevated do have an apparent long-term remission. However, there is no support from the study of Atkinson for use of a cut-off value of cortisol (or ACTH) to study patients.

There are a substantial number of other studies that examine post-operative outcomes following treatment of Cushing's disease (these are reviewed by Atkinson). Three relatively recent ones from the UK represent single-centre experience and are, therefore, comparable to the paper by Acebes. Reese and colleagues assessed endocrine function "within one week" of surgery and reported that baseline cortisol that was undetectable was a good predictor of immediate remission [2]. However, they did note that two patients who relapsed also showed undetectable baseline cortisol levels. In a study from Oxford, Yap and colleagues assessed endocrine function between three and four days after pituitary surgery, having withdrawn any steroid supplements 24 hours beforehand [3]. They concluded that an undetectable post-operative cortisol was not invariably associated with long-term remission in Newcastle, Chee and colleagues assessed endocrine function six to eight weeks after pituitary surgery using a thorough evaluation of pituitary adrenal function [4]. They concluded that there was a wide overlap between subjects who were in remission and those who relapsed, although mean cortisol levels in the remission group were lower than in those who had relapsed. These studies, between them, include a substantial number of patients and represent, collectively, extensive experience in post-operative assessment of Cushing's disease. The message that they contain is consistent with that of Acebes; it is clear that some patients following pituitary surgery will achieve remission despite having easily detectable baseline cortisol measurements. The reason for this is not clear – the adrenal cortex in patients with severe Cushing's disease will, of course, be hyperplastic and will be exquisitely sensitive to very small amounts of ACTH, possibly produced in the adrenal, that may act in a paracrine manner to sustain cortisol synthesis. In some circumstances there may, indeed, be semi-autonomous cortisol production due to adrenal nodule formation. In this circumstance successful removal of an ATCH-producing adenoma may not, immediately, lead to rapid decline of adrenal cortisol production.

However, the other finding from the cumulative studies in the United Kingdom showed that a very low cortisol level post-operatively is not

always predictive of long-term remission was not reported by Acebes. Indeed, all of the patients in the present series who failed to achieve remission had high cortisol levels and those with very low values were in apparent remission. This discrepancy may be due to several factors. Firstly, Acebes and colleagues measured cortisol very early after surgery and all of the other studies performed measurements slightly later (generally between three days and six weeks post-operatively). The duration of follow-up by Acebes and colleagues was relatively short in comparison to the other studies and it may not be safe to assume that all of the patients whom they classified as being in remission will ultimately remain so in the long-term. Finally, the biochemical assessment by Acebes and colleagues was relatively insensitive – they relied on measurement of urinary cortisol excretion to identify potential relapse but did not perform studies of cortisol diurnal rhythm or of Dexamethasone suppressability. Had they done so they might have identified early relapse in some of their subjects.

In summary, therefore, what are we to make of this paper? The authors have confirmed that a high remission rate can be achieved in a single centre with an experienced Neurosurgeon operating on patients. They have shown that there is a wide range of cortisol measurements in patients following surgery and that there is substantial overlap between those who achieve remission and those who fail to be cured. Although, statistically, they have shown a cut-off level of cortisol that can differentiate the two groups, the practical value of this remains unclear – the message, ultimately, must be that individual patients need to be managed by a combination of careful clinical and biochemical evaluation. Perhaps the simplest message is that surgical cure is most likely to be achieved if a distinct ACTH-producing adenoma has been identified at the time of operation and its presence confirmed histologically.

References

1. Atkinson AB, Kennedy A, Wiggam MI, McCance DR, Sheridan B (2005) Long-term remission rates after pituitary surgery for Ching's disease; the need for long-term surveillance. Clin Endocrinol 63: 549–559
2. Rees DA, Hanna FWF, Davies JS, Mills RG, Vafidis J, Scanlon ME (2002) Long-term follow-up results of transsphenoidal surgery for Cushing's disease in a single centre using strict criteria for remission. Clin Endocrinol 56: 541–553
3. Yap LB, Turner HE, Adams CBT, Wass JAH (2002) Undetectable post-operative cortisol does not always predict long-term remission in Cushing's disease: a single centre outcome. Clin Endocrinol 56: 25–31
4. Chee GH, Mathias DB, James RA, Kendall-Taylor P (2001) Transsphenoidal pituitary in Cushing's disease: can we predict outcome? Clin Endocrinol 33: 525–537

John M. C. Connell
Glasgow

Correspondence: Juan Martino, Department of Neurosurgery, Hospital Universitario de Bellvitge, Feixa Llarga s/n, 08907, L'Hospitalet de Llobregat, Barcelona, Spain. e-mail: 37055jmg@comb.es