

Commentary

Early assessment of outcome of pituitary surgery for Cushing's disease

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In recent years selective pituitary adenectomy by transphenoidal microsurgery has become the treatment of choice for Cushing's disease. However, it is not successful in all patients. Recently, the European Cushing's Disease Survey Study Group has reported on 668 patients with Cushing's disease from 25 institutions throughout Europe treated with transsphenoidal surgery between 1975 and 1990 (Bochicchio *et al.*, 1995). Early clinical and biochemical remission of hypercortisolism after surgery occurred in 76.3% of patients. Unfortunately, not all of the patients in remission after surgery were really cured: the disease recurred at a mean time of 39.3 months in 12.7% of 510 patients who were in remission after the operation. The distribution of the recurrences did not show any plateau or cluster throughout the follow-up period, so it may be expected that with longer follow-up more relapses will be observed.

Accurate early assessment of outcome of pituitary surgery for Cushing's disease is important to expedite further treatment in patients with persistent hypercortisolism. Patients in whom the morning serum cortisol level and/or 24-hour urinary cortisol excretion are above the normal range in the early postoperative period (5–14 days of surgery) are considered surgical failures. They have to be referred for further treatment, e.g. early repeat surgery (Ram *et al.*, 1994) or pituitary irradiation (Estrada *et al.*, 1997). On the contrary, the finding of a morning serum cortisol level and 24-hour urinary cortisol excretion clearly below normal, especially when accompanied by symptoms of secondary adrenocortical insufficiency, will almost invariably be followed by a clinical remission of Cushing's disease. However, a small number of patients in whom pituitary surgery induces a remission of the disease are not hypocortisolaemic immediately after surgery: serum cortisol may decline only gradually to a level below normal in patients with adrenal macronodules and a period of hypocortisolaemia after surgery may even be lacking completely in patients with periodic hypersecretion of cortisol or in those receiving medical treatment to lower their cortisol production before surgery (Friedman & Chrousos, 1993). Therefore, when in the immediate postoperative period the morning serum cortisol level and 24-hour urinary cortisol excretion are in the normal

range or when one of these parameters is normal and the other below normal, the conclusion that surgery has failed is not necessarily justified. In a substantial number of these patients an early clinical remission may be observed (Vignati *et al.*, 1994) and some of them may be really cured. Caution is also needed in the interpretation of the low-dose dexamethasone test postoperatively. Failure to suppress with dexamethasone in the early postoperative period, but normal suppressibility later, and a course compatible with cure have been reported (McDonald *et al.*, 1978). On the other hand, persistent Cushing's disease after operation, despite full suppression with dexamethasone, has also been described (Jeffcoate *et al.*, 1985). Furthermore, a normal postoperative low-dose dexamethasone test certainly does not exclude a late relapse of the disease (Vignati *et al.*, 1994).

Biochemical testing in the immediate postoperative period is also valuable as an early marker of the risk of relapse. Patients who relapse after an initial remission have significantly higher morning serum cortisol levels, as well as 24-hour urinary cortisol excretion in the immediate postoperative period than patients who do not relapse. However, there is considerable overlap between values recorded in patients who do and those who do not relapse (Pieters *et al.*, 1989; Vignati *et al.*, 1994). It has been claimed that the finding of ACTH hyperresponsiveness in an early postoperative CRH test is more valuable for identifying patients at risk of recurrence of Cushing's disease than measurement of basal cortisol levels (Vignati *et al.*, 1994). Again, however, there is considerable overlap in responses between patients who do and those who do not relapse. The strongest predictor of cure seems to be the finding of an undetectable serum cortisol level in the immediate postoperative period. No recurrences were reported in 2 recent series (median time of follow-up 40 and 90 months, respectively) in patients who had undetectable serum cortisol levels in the immediate postoperative period (Trainer *et al.*, 1993; McCance *et al.*, 1993). This was not found in the European multicentre study, in which the disease recurred during follow-up in 4.3% of patients with undetectable circulating cortisol levels postoperatively (Bochicchio *et al.*, 1995). However, information on the detection limits and other performance characteristics of the cortisol assays used in the participating centres was not given in this study.

The study of Van Aken *et al.*, (1997) confirms the limitations of the morning serum cortisol level and the 24-hour urinary cortisol excretion in the immediate postoperative period as predictors of the early and late outcome of pituitary surgery for

Cushing's disease. Early remission of Cushing's disease was seen in a few patients with a normal morning serum cortisol level or normal 24-hour urinary cortisol excretion. Furthermore, serum and urinary cortisol levels in the immediate postoperative period were in the same range in the 3 patients who had a relapse of Cushing's disease after an initial remission as in the patients who remained in remission. Interestingly, in the study of Van Aken *et al.*, the metyrapone test completely separated patients who had an early remission of Cushing's disease after pituitary surgery and those who had not. Moreover, the metyrapone test was useful for the early detection of patients at risk of a relapse: all 3 patients who had a recurrence of Cushing's disease had a serum 11-deoxycortisol level >150 nmol/l after metyrapone and of 14 patients who remained in remission only one had a serum 11-deoxycortisol level >150 nmol/l after metyrapone. Although these results are promising, it concerns a retrospective study in which only 29 of 77 consecutive patients were included and median follow-up was only 35 months.

No single diagnostic test can separate all patients with untreated Cushing's disease from healthy subjects. Similarly, it is doubtful whether in the postoperative period 1 single test will be able to assess reliably the early outcome of pituitary surgery for Cushing's disease and to predict all recurrences of the disease. Prospective studies with a large number of patients and long follow-up times are needed to determine which combination of clinical and laboratory data will come close to this goal.

References

- Aken, M. van, Herder, W. den, Lely, A.J. van der, Jong, F. de. & Lamberts, S. (1997) Postoperative metyrapone test in the early assessment of outcome of pituitary surgery for Cushing's disease. *Clinical Endocrinology*, **47**, 145–149.
- Bochicchio, D., Losa, M., Buchfelder, M. & the European Cushing's Disease Survey Study Group (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. *Journal of Clinical Endocrinology and Metabolism*, **80**, 3114–3120.
- Estrada, J., Boronat, M., Mielgo, M., Magallón, R., Millán, I., Diez, S., Lucas, T. & Barceló, B. (1997) The long-term outcome of pituitary irradiation after unsuccessful transsphenoidal surgery in Cushing's disease. *New England Journal of Medicine*, **336**, 172–177.
- Friedman, T. & Chrousos, G. (1993) Transsphenoidal resection in Cushing's disease: definition of success. *Clinical Endocrinology*, **39**, 701.
- Jeffcoate, W., Dauncey, S. & Selby, C. (1985) Restoration of dexamethasone suppression by incomplete adenectomy in Cushing's disease. *Clinical Endocrinology*, **23**, 193–199.
- McCance, D., Gordon, D., Fannin, T., Hadden, D., Kennedy, L. & Atkinson, A. (1993) Postoperative data: which early tests best predict longterm remission? *Journal of Endocrinology*, **139** (Suppl. 1), 13.
- McDonald, S., Van Hofe, S., Dorfman, S., Jordan, R., La Morgese, J. & Young, R. (1978) Delayed cure of Cushing's disease after transsphenoidal surgery of pituitary microadenomas. *Journal of Neurosurgery*, **49**, 593–596.
- Pieters, G., Hermus, A., Meijer, E., Smals, A. & Kloppenborg, P. (1989) Predictive factors for initial cure and relapse rate after pituitary surgery for Cushing's disease. *Journal of Clinical Endocrinology and Metabolism*, **69**, 1122–1126.
- Ram, Z., Nieman, L., Cutler, G., Chrousos, G., Doppman, J. & Oldfield, E. (1994) Early repeat surgery for persistent Cushing's disease. *Journal of Neurosurgery*, **80**, 37–45.
- Trainer, P., Lawrie, H., Verhelst, J., Howlett, T., Lowe, D., Grossman, A., Savage, M., Afshar, F. & Besser, G. (1993) Transsphenoidal resection in Cushing's disease: undetectable serum cortisol as the definition of successful treatment. *Clinical Endocrinology*, **38**, 73–78.
- Vignati, F., Berselli, M. & Loli, P. (1994) Early postoperative evaluation in patients with Cushing's disease: usefulness of ovine corticotropin-releasing hormone test in the prediction of recurrence of disease. *European Journal of Endocrinology*, **130**, 235–241.