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Commentary

Transsphenoidal surgery for Cushing's disease: defining cure and following outcome*

John Newell-Price
Division of Clinical Sciences, University of Sheffield, Northern General Hospital, Sheffield Teaching Hospitals, Herries Road, Sheffield, UK

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Ideally, selective and complete removal of a corticotroph adenoma should cure Cushing's disease and leave no other pituitary dysfunction. Furthermore, endocrinologists should be in a position to inform patients with Cushing's disease whether they are cured following transsphenoidal surgery. As with diagnosis of this condition, however, definition of cure continues to be debated. Such definition is dependent on ultimate outcome, a classification that may only be made with careful and long-term follow-up. It has been suggested that the relapse rate following successful surgery ranges from 0 (McCance *et al*., 1993, 1996; Trainer *et al*., 1993) to 17% (Invitti *et al*., 1999). Such differences in relapse rates are likely to be explained largely by the classification of patients into 'cure', remission or persistence of disease in the postoperative period. Cushing's disease is a rare condition and even in major endocrine centres it takes many years for the number of patients to accumulate and be large enough for meaningful retrospective analyses to be made. Moreover, the utility of the various parameters that might be useful in predicting a favourable outcome such as identification of tumour on imaging or at surgery, and by histological confirmation remain controversial.

It is against this setting that two series of patients undergoing transsphenoidal surgery for Cushing's disease are published in this journal (Chee *et al*. 2001; Yap *et al.* (2001). A strength of these studies is that they are from major UK endocrine centres, each with surgery performed by a single highly experienced pituitary surgeon. Detailed long-term follow-up data on 97 patients are reported from the Oxford Group and on 61 by the Newcastle Group, with mean (and median) follow-up periods of 92 (38) and 88 (N/A) months, respectively. Diagnostic criteria, predictors of outcome and markers of 'cure' or remission are carefully analysed.

Because patients with ectopic adrenocorticotropic hormone (ACTH) secretion are not reported, the results of the biochemical tests used for diagnosis can only be assessed in terms of sensitivity for the presence of Cushing's disease. In this respect, the results of the low-dose dexamethasone-suppression test (96–97%) and urinary free cortisol estimations (UFC) (100%) are in keeping with published data (Newell-Price *et al*., 1998). It should be remembered, however, that UFC measurements have a relatively low specificity, being frequently elevated in other conditions such as the polycystic ovarian syndrome and depression. Interestingly, the Newcastle data indicate very good results from high-dose dexamethasone testing: 31/32 and 30/33 of patients tested suppressed UFC or serum cortisol by more than 50%, giving sensitivities of 96% and 90%. This is better than other larger series, but it is conceivable that the sensitivity might decrease as more patients are investigated. Caution should be applied to the interpretation of the corticotrophin-releasing hormone (CRH) tests reported in these studies as the numbers of patients who had the tests are small, and in the Oxford series it is unclear as to how many patients received human sequence or ovine sequence CRH. This is important as the responses to these peptides differ quantitatively, and response criteria derived for one peptide are not necessarily applicable to the other. Bilateral inferior petrosal sinus sampling (BIPSS) was used infrequently in both series and this may explain the relatively poor results reported here for this investigation. Analysis of large series data indicates that BIPSS is the most reliable discriminator between pituitary and ectopic origins of ACTH secretion, with an overall sensitivity of 96% and specificity of 100% when performed on patients in the hypercortisolaemic state (Oldfield *et al*., 1991; Kaltsas *et al*., 1999; Newell-Price *et al*.,1998).

In the immediate surgical period there was only one death in total (from a myocardial infarct in the larger Oxford series), confirming the relative safety of transsphenoidal surgery. The incidence of other serious complications was low. Differences between the series include a better outcome if a tumour was identified both on imaging and histologically in the Newcastle series, whilst identification on imaging made no difference in the Oxford series. Macroadenomas recurred more frequently than microadenomas in the Oxford series, a difference not noted in the Newcastle series, and whilst increased surgical experience over time improved outcome in Oxford, in Newcastle the outcome was similar regardless of time cohort analysed. In both series, the incidence of other long-term pituitary dysfunction postoperatively is higher than that

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Correspondence: J. Newell-Price, Division of Clinical Sciences, University of Sheffield, Northern General Hospital, Sheffield Teaching Hospitals, Herries Road, Sheffield S5 7AU, UK.
E-mail: j.newell-price@sheffield.ac.uk

following surgery for acromegaly, and this may reflect the will to try and achieve cure in Cushing's disease.

The criteria used to define cure or remission by the two groups vary and highlight debate in this area. The Oxford group have analysed their data in terms of outcome compared to the postoperative morning cortisol, measured within 2 weeks of surgery, whilst the Newcastle group used a combination of circadian rhythm studies, UFC and dexamethasone-suppression data at 2 and 6 weeks postoperatively. Details are not given of the dosage of glucocorticoid administered in the postoperative period prior to assessment, and this may be of some considerable significance when interpreting the results of outcome. The Newcastle series reports recurrence in 7/48 (14·5%) of patients initially deemed to be in remission, at a mean of 76 months. This compares favourably with the recent Italian multicentre study in which the overall relapse rate in 288 patients following pituitary surgery was 17% (Invitti *et al*., 1999). It is possible that this reflects less stringent criteria for the definition of cure or remission in the latter study. If one accepts that Cushing's disease is due to a single autonomous corticotroph adenoma, then discrete and complete surgical excision should result in undetectable postoperative cortisol values, since the remaining normal corticotroph cells will be suppressed (often for several years). However, in the series reported by Bochicchio *et al*. (1995) of patients undergoing surgery for Cushing's disease, 510 had normal postoperative dexamethasone-suppression tests, of which 65 (12·7%) suffered a recurrence, whilst in the 94 patients with undetectable postoperative morning cortisol values, the recurrence rate was 4·3%. This huge multicentre survey indicates that dexamethasone testing is a blunter instrument to define cure/remission, but recurrence after an undetectable postoperative serum cortisol is of concern. Moreover, in the Oxford series, 7/61 (11·5%) patients in whom the postoperative serum cortisol had been < 50 nmol/l suffered a recurrence at a mean of 36 months. These data are in contrast to existing data from two centres (McCance *et al*., 1993; Trainer *et al*., 1993) and an update from the latter centre presented in 1997 (albeit in abstract form): 60/103 patients (58%) with postoperative 09·00 h serum cortisol values of < 50 nmol/l exhibited no biochemical or clinical recurrence, with a median follow-up of 58 months (2–126) (Newell-Price *et al*., 1997). In 2001, none of these or subsequent patients deemed cured by the same criterion have suffered a clinical or biochemical relapse on repeated assessment over now even longer follow-up. As such, this stringent criterion does genuinely appear to indicate long-term cure. The manner of assessment may be critical since the serum cortisol was < 50 nmol/l on at least two occasions, and was measured within a few days of operation with avoidance of glucocorticoid therapy from 24 h after surgery for microadenomas, unless clinically indicated. Interestingly, if we include the seven 'relapses' in the failed group from Oxford then the cure rate is almost identical at 56% (54/97). Although patients were assessed by different means in Newcastle, if no further relapses are observed in the future then their remission rate is high at 67% (41/61), and it will be interesting to see if this is maintained as greater numbers are treated and followed.

How can we account for the discrepancies? There is a danger of trying to explain away differences in outcome data to leave a neat hypothesis intact. Given this caveat, there is potentially a very rational explanation for the differences in relapse observed following the initial postoperative classification based on postoperative 09·00 h serum cortisol values. Glucocorticoids exquisitely inhibit the synthesis and release of ACTH, at both hypothalamic and pituitary level. At the level of pro-opiomelanocortin gene (the peptide product of which is cleaved to ACTH), transcription in corticotroph cells is inhibited within only 15 min of glucocorticoid exposure (Eberwine & Roberts, 1983). Even in pathological states, such as Cushing's disease, at least 2% of patients with active corticotroph tumours show full suppression of plasma cortisol on a LDDST, indicating relative sensitivity to glucocorticoids. Therefore, in the postoperative setting, synthesis and release of ACTH can be inhibited from a few remaining corticotroph tumour cells if glucocorticoids are administered, even at low doses, and especially for extended periods of time (days to weeks). As such, some patients with Cushing's disease treated with glucocorticoids in the postoperative period may have plasma cortisol values of < 50 nmol/l when measured, but still go on to recur as remaining tumour cells grow slowly over the years of follow-up. In reality these were never 'cured'.

As an alternative, prediction of risk of relapse by utilization of desmopressin testing in Cushing's disease is also published in this Journal. Losa & co-workers (2001) report a large series of 107 patients with Cushing's disease, and confirm the poor sensitivity of this test for the diagnosis of Cushing's disease: an ACTH response was seen in 84% and a cortisol response in only 78·5%, below the pretest likelihood of Cushing's disease in ACTH-dependent Cushing's syndrome. The authors also sought to test the hypothesis that cure might be indicated by loss of plasma ACTH and serum cortisol responses to desmopressin postoperatively in those patients in whom there had been a response preoperatively. The authors are very careful to acknowledge the potential confounding effects of administered glucocorticoid in the immediate postoperative period on the classification of patients into cure, remission and failed groups. Following surgery, 50/87 patients tested pre- and postoperatively demonstrated disappearance of an ACTH response to desmopressin in the postoperative period. However, of these, four were immediate surgical failures. In contrast, 18 of 37 with a response postoperatively were

deemed to be in remission (as assessed on dexamethasone-suppression testing). Interestingly, of these, three relapsed after 24, 38 and 54 months. Longer follow-up is needed but their preliminary data indicate that persistence of an ACTH response to desmopressin might be associated with a higher rate of relapse. However, the positive predictive value of this test will be low unless the remaining 15/18 patients in this group all relapse on further follow-up, and the test would seem more cumbersome than assessment of 09·00 h serum cortisol.

All these studies agree on the importance of long-term follow-up of this challenging condition. Whilst transsphenoidal surgery for Cushing's disease remains the primary definitive treatment option, even in major endocrine centres the overall outcome is still somewhat disappointing. None of these studies address the difficult issue of how best to manage those patients with low normal cortisol values following pituitary surgery. Moreover, given the complexity of investigation, the results of surgery even in experienced hands, and the requirement for rigorous long-term follow-up, there can be no place for management of Cushing's disease by the occasional endocrinologist nor by the occasional pituitary surgeon.

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