

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

DOMENICO BOCHICCHIO, MARCO LOSA, MICHAEL BUCHFELDER, AND
THE EUROPEAN CUSHING'S DISEASE SURVEY STUDY GROUP*

Institute of Endocrine Sciences, Ospedale Maggiore IRCCS (D.B.), and Department of Neurosurgery, Ospedale San Raffaele IRCCS (M.L.), University of Milan, Milan, Italy; and Department of Neurosurgery, University of Erlangen-Nürnberg (M.B.), Erlangen, Germany

ABSTRACT

Hypercortisolism attributable to hypersecretion of ACTH by a pituitary adenoma is an uncommon and progressively lethal disease. Because of its rarity, it has been difficult to collect a large series of patients in order to identify the prognostic factors influencing the outcome after transsphenoidal surgery. We conducted a multicenter, retrospective analysis of the early and late results of surgical treatment of Cushing's disease.

Files of patients with Cushing's disease who underwent transsphenoidal surgery between 1975 and 1990 were collected from 25 institutions throughout Europe. Data from 668 of 716 patients were suitable for statistical analyses. Surgical mortality was 1.9%, and major morbidity occurred in 97 patients (14.5%). Clinical and biochemical remission of Cushing's disease after surgery occurred in 510 cases (76.3%). Identification of the tumor by neuroradiological imaging or at operation with histopathological corroboration was associ-

ated with remission of hypercortisolism. Recurrence of the disease occurred in 65 (12.7%) of 510 patients in remission after surgery at a mean time of 39.3 months (range 6–104 months). The distribution of the recurrences did not show any apparent plateau or cluster throughout the follow-up period. Low postoperative steroid levels, absence of cortisol response to CRH, and the need for long-term glucocorticoid substitution therapy were all associated with a high probability of long-term remission.

Our study demonstrates that transsphenoidal surgery is a safe and effective treatment for patients with Cushing's disease. However, after successful surgery there is a steady increase in the percentage of recurrences, which continues with time. Patients who after operation had hypoadrenocorticism and needed long-term glucocorticoid substitution therapy had the lowest risk of relapse. (*J Clin Endocrinol Metab* 80: 3114–3120, 1995)

HYPERCORTISOLISM attributable to overproduction of ACTH by a pituitary adenoma (Cushing's disease) is rare. Its incidence in the general population is estimated to

be between 0.7 and 2.4 cases/million inhabitants per year (1, 2). In most patients, hypercortisolism leads to severe complications and is associated with premature mortality if left untreated. At this time, microsurgical removal of the pituitary adenoma is the treatment of choice for Cushing's dis-

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Address all correspondence and requests for reprints to: Dr. Domenico Bochicchio, Istituto di Scienze Endocrine, Ospedale Maggiore di Milano IRCCS, Via Francesco Sforza 35, 20122 Milano, Italy.

* European Cushing's Disease Survey Study Group: A. Stevenaert, Department of Neurosurgery, A. Beckers, Department of Endocrinology, Hôpital Universitaire du Sart Tilman, Liège, Belgium; C. Hagen, Department of Internal Medicine and Endocrinology, P. Bjerre, Department of Neurosurgery, Odense University Hospital, Odense, Denmark; A. Kruse and J. Lindholm, Department of Neurosurgery, University Hospital Rigshospitalet, Copenhagen, Denmark; R. Fahlbusch, Department of Neurosurgery, University of Erlangen-Nürnberg, Erlangen, Germany; O. A. Müller, Department of Internal Medicine, Rotkreuz-Krankenhaus, Munich, Germany; K. von Werder, Department of Internal Medicine, Schloßpark Klinik, University of Berlin, Berlin, Germany; B. Ambrosi and G. Faglia, Institute of Endocrine Sciences, Ospedale Maggiore IRCCS, University of Milan, Milan; M. Giovanelli, Department of Neurosurgery, Ospedale San Raffaele IRCCS, University of Milan, Milan, Italy; A. Angeli, Department of Internal Medicine II, University of Turin, Orbassano-Turin, Italy; G. Maira, Department of Neurosurgery, Policlinico Gemelli, University Cattolica del Sacro Cuore, Rome, Italy; G. F. F. M. Pieters, Department of Medicine, Division of Endocrinology, St. Radboud University Hospital, Nijmegen, The Netherlands; D. Carvalho (coordinator), J. L. Medina, Department of Endocrinology, Hospital de San João, Porto, Portugal; C. Costa, Department

of Endocrinology, Hospital Curry Cabral, Lisboa, Portugal; A. Galvão Teles, Department of Endocrinology, Hospital de St. Maria, Lisboa, Portugal; L. Guerreiro, Department of Endocrinology, Hospital Egas Moniz, Lisboa, Portugal; M. Ruas, Department of Endocrinology Hospitais da Universidade de Coimbra, Coimbra, Portugal; I. Salcedo, Department of Endocrinology, Hospital Geral de St. António, Porto, Portugal (under the patronage of the Portuguese Society of Endocrinology, President E. Peres); V. Dolenc and M. Jezernik, Department of Neurosurgery, University of Ljubljana, Ljubljana, Slovenia; J. A. Vázquez and S. Gaztambide, Hospital de Cruces, Baracaldo-Vizcaya, Bilbao, Spain; S. M. Webb, Hospital de S. Creu i S. Pau, Barcelona, Spain; I. Halperin and E. Vilardell, Hospital Clínic i Provincial, Barcelona, Spain; O. Vidal, Hospital Canalejo, La Coruña, Spain; F. Sánchez-Franco, Centro de Salud Carlos III, Madrid, Spain; R. Astorga, A. Leal-Cerro, P. P. García Luna, and E. Torres, Hospital Virgen del Rocío, Sevilla, Spain; M. Thorén and S. Werner, Department of Endocrinology and Metabolism, Karolinska Hospital, Stockholm, Sweden; A. M. Landolt, Department of Neurosurgery, AMI Klinik, Zurich, Switzerland; A. B. Atkinson, D. R. McCance, D. S. Gordon, D. R. Hadden, and L. Kennedy, Metabolic Unit, Royal Victoria Hospital, Belfast, Northern Ireland, UK; M. F. Scanlon, Department of Medicine, College of Medicine, University of Wales, Cardiff, Wales, UK; G. Cruickshanks and G. M. Teasdale, Institute of Neurological Sciences, Southern General Hospital, Glasgow, Scotland, UK.

ease (3). Other therapeutic options, such as bilateral adrenalectomy (4, 5), medical therapy with adrenostatic drugs (6), radiotherapy (7), and radiosurgery (8), have been proposed either as alternatives to pituitary surgery or as adjunctive therapy in cases of incomplete remission of the disease after operation. In the last decade, several institutions have reported the results of transsphenoidal surgery in patients with Cushing's disease. Although most authors describe a remission rate of 70–90%, the only other available retrospective multicenter survey reported considerably less favorable results in centers in the United States (9). Moreover, an increasing rate of late recurrence of the disease to as high as 20% at 5–6 yr has been reported, especially in those series with the longest follow-up (10–13). The rarity of Cushing's disease has precluded the collection of a large series of patients undergoing transsphenoidal operation in the same institution, thus making it difficult to assess the preoperative and postoperative factors influencing the immediate and late outcome of the disease. To address this problem, we carried out a retrospective, multicenter study in European countries in order to gather enough patients who had undergone surgery for Cushing's disease, thus allowing us to perform a meaningful analysis of the possible prognostic factors linked to either failure or recurrence.

Materials and Methods

Study design

Endocrine and neurosurgical centers throughout Europe were asked to participate in a retrospective study on the surgical treatment of Cushing's disease; a study protocol was elaborated, discussed, and amended by all participants, and a questionnaire was prepared accordingly (a copy is available on request).

All consecutive patients at each center were included in the study when the following criteria were met: 1) planned transsphenoidal surgery for suspected Cushing's disease. Criteria for the diagnosis of Cushing's disease were not explicitly given because of the great variability of the diagnostic tests used in the different countries during the period of the study. However, from a survey conducted among the participating centers, patients were diagnosed to have Cushing's disease on the basis of at least the clinical picture and the lack of steroid suppression during low-dose dexamethasone administration. Patients for whom an operation had been scheduled but not completed because of technical failure or patients who were later found to harbor an ectopic ACTH-secreting tumor were also included on an intention-to-treat basis; 2) operation performed between January 1, 1975, and December 31, 1990. The former limit was chosen because microsurgical removal of pituitary tumors was not common before 1975; and 3) no prior pituitary surgery.

The questionnaire had five sections. The first contained the general demographic data of the patient and the presumed year of onset of the disease. The second section contained endocrinological data (baseline cortisol, ACTH, and urinary steroid levels; ACTH and steroid responses to TRH/GnRH and to corticotropin-releasing hormone (CRH) administration; and results of bilateral inferior petrosal sinus sampling) and neuroradiological characteristics [plain skull radiography, computed tomography (CT) scan, and magnetic resonance imaging (MRI)]. The third section concerned surgical characteristics (date of surgery, type of surgery, and diameter, location, invasiveness, and histological confirmation of a pituitary lesion), early endocrinological postoperative evaluation, and the need for and the duration of postoperative glucocorticoid substitution therapy. The fourth section referred to the last available follow-up information (date of last visit; baseline cortisol, ACTH, and urinary steroid levels; present status of the patient and in the case of death, date and cause). If the patient had a clinical and biochemical recurrence of Cushing's disease after successful operation, participants were asked to complete the fifth section of the questionnaire concerning

the endocrinological and neuroradiological characteristics of the patient at relapse.

Hormonal data were described qualitatively as high, normal, or low according to the reference limits applied in each center. Similarly, responses to stimulation tests were described as normal, high, or no response, as the large time span of the study and the different methods used throughout Europe for the measurement of hormone levels prevented the possibility of any meaningful quantitative analysis. However, to keep the results as homogeneous as possible, general criteria for determining normal and pathological responses were given. Thus, an increment of ACTH levels of at least 50% over baseline or an increase of cortisol concentrations of at least 160 nmol/L after the administration of TRH/GnRH or both were required to define a paradoxical response to this test. Participants were requested to specify the criteria they used for classifying the response to the CRH test (ovine or human). ACTH and cortisol increments lower than 50% over baseline after CRH administration were regarded as indicating no response. There was more variability in the definition of the upper normal limit because this is usually derived from data in normal controls tested in each center. Therefore, the classification of the response given by each investigator was usually accepted. The results of bilateral inferior petrosal sinus sampling included the study of both basal and CRH-stimulated ACTH secretion in most cases. Because at the time the study was planned no patient with the ectopic ACTH-syndrome was known to show a baseline ACTH ratio greater than 1.4 between the petrosal sinus levels and the peripheral venous concentrations, this value was regarded as indicative of pituitary-dependent hypercortisolism (14, 15). The same value has been used to indicate the presence of a left or right gradient at the pituitary level (15).

A detailed explanation of all definitions given in the questionnaire was included. All of the questionnaires received were individually checked for inconsistencies before statistical analysis.

Statistical analysis

The major goal of the study was to detect the main prognostic factors linked to either failure of treatment or recurrence of Cushing's disease after transsphenoidal surgery. For this reason, analysis of the data was divided in two parts. In the first, the response of patients was categorized as either treatment failure, *i.e.* patients who needed additional therapy for persisting clinical and biochemical hypercortisolism, or as treatment success, *i.e.* patients who did not need any additional treatment as they showed clinical remission of the disease and return of a normal suppression of steroid levels during low-dose administration of dexamethasone. If recurrence of the disease occurred within 6 months after surgery, patients were considered as treatment failure.

In the second part, we focused on the recurrence of Cushing's disease. In this analysis we included only patients who were classified as treatment success after surgery (see above). They were then subdivided into patients who had a relapse and those who did not have evidence of relapsing Cushing's disease until the last follow-up visit.

Quantitative variables are expressed as mean \pm SEM. Qualitative data were analyzed by the χ^2 statistic without Yates' correction. Quantitative variables were analyzed by the Mann-Whitney test to avoid assumption about the gaussian distribution.

The occurrence of relapse is related to the length of follow-up; therefore, the cumulative probability of no relapse during the follow-up was estimated by means of survival analysis [product-limit method according to Kaplan and Meier (16)]. The differences in the disease-free experience among the classes of the investigated variables were tested by Breslow generalized Wilcoxon test (17).

To obtain reliable estimates, the disease-free curve was stopped at 120 months, which is when the number of patients remaining at risk was approximately less than 5% of the starting sample. As some information was not gathered at the time of original diagnosis or treatment, missing data were dealt with by carrying out complete case analyses in which patients were excluded from particular analyses if their files did not contain data on the required variables.

Results

Patient characteristics

The total number of questionnaires received was 716. After careful scrutiny of the data, 668 forms were retained for final analysis. The reasons for exclusion of the remaining 48 questionnaires were the following: patients actually had Nelson's disease ($n = 10$); patients had been operated on after the date for inclusion in the study ($n = 12$); and important data were missing ($n = 26$). A clear preponderance of female patients was observed (female/male ratio: 3.32). Mean age at surgery was 38.2 ± 0.55 yr (range 8–84 yr, median 38 yr). The estimated interval between onset of the disease and diagnosis of Cushing's disease was 53.3 ± 1.82 months (range 5–355 months, median 40), and the mean interval between diagnosis and surgery was 10.2 ± 1.05 months (range 1–342 months, median 3.4 months). Surgery was performed before 1981 in 95 patients (14.2%), between 1981 and 1985 in 277 patients (41.5%), and after 1985 in 296 patients (44.3%).

Mortality and morbidity

Perioperative mortality was defined either as any death occurring within 1 month from surgery or as death resulting from a complication of operation. The perioperative mortality rate was 1.9% (13 patients). Death occurred between 5 and 134 days after operation. Of the patients who died, 3 were operated on before 1981 (3.2%), 6 were operated on between 1981 and 1985 (2.2%), and 4 were operated on after 1985 (1.4%). Major complications of surgery were reported in 97 patients (14.5%) and were distributed unevenly among cured and not cured patients. The most frequent adverse events were cerebrospinal fluid rhinorrhea (4.6%), diabetes insipidus for at least 6 months (3.0%), meningitis (2.8%), vascular injury or profuse bleeding (1.3%), and pulmonary embolism (0.6%). Twenty-two patients experienced 2 or more complications. The most frequent association was meningitis after postoperative cerebrospinal fluid rhinorrhea (7 patients).

Early postoperative results

After operation, 158 patients (23.7%) were considered as treatment failure and 510 (76.3%) were judged to be in remission. The percentage of failure varied among the different centers from 0% to 47.6% (median 18.2%). When considering only centers with at least 20 evaluable patients, the failure rate ranged from 7.4%–47.6% (median 14.6%). No significant association was found between the general demographic characteristics of the patients and the occurrence of failure. There was a nonsignificant trend toward a declining percentage of surgical failures in more recent years (28.4%, 25.6%, and 20.3% for the periods 1975–1980, 1981–1985, and 1986–1990, respectively). Previous therapy with drugs, radiotherapy, and partial adrenalectomy, alone or in combination, reported in 176 patients (26.5%), did not correlate with the outcome.

Baseline ACTH, cortisol, and urinary steroid levels were not associated with the outcome of surgery. Preoperative dynamic testing of ACTH and cortisol secretion with CRH and TRH/GnRH was reported in 208 and 100 patients, re-

spectively. Patients with normal or excessive ACTH and cortisol response to CRH showed a failure rate (22.9%) that was significantly lower than in the group with no response (44.0%; $P < 0.05$). The presence of a paradoxical increase of cortisol levels after TRH/GnRH administration, reported in 27 patients (27%), had a near-significant negative prognostic value (percentage of failure in this group 37% vs. 20.5% in the group without such response; $P < 0.10$).

Bilateral sampling of inferior petrosal sinus was performed in 98 patients. The overall failure rate in this group (23.5%) was similar to that of patients who did not undergo the procedure (23.7%). Seventeen patients did not show a positive central-peripheral gradient but they were subjected to surgery nonetheless; 6 of them did not achieve remission of the disease. In the 3 patients lacking histological confirmation of a pituitary adenoma, an ectopic ACTH-syndrome was strongly suspected. However, at the last follow-up (4, 35, and 40 months after surgery), no source of ectopic ACTH secretion was detected. In the patients with a gradient, the percentage of failure was significantly higher in patients who did not have a left or right gradient (50%) than in those who did have a left or right gradient (13.3% and 17.9%, respectively; $P < 0.05$).

Visualization of the adenoma by CT, reported in 281 (47.7%) of 589 patients, was strongly correlated with a good outcome (failure rate of 14.9% as compared to 28.4% and 29.7% of patients with normal or equivocal findings, respectively; $P < 0.001$). Analysis of MRI, although performed in only 115 patients, confirmed a similar trend (failure rate of 12.9% in patients in whom the adenoma was identified vs. 26.4% in patients with no evidence of the tumor; $P < 0.10$).

Selective adenectomy, selective adenectomy with wide margins, and hemihypophysectomy had similar failure rates of 20.0%, 23.8%, and 19.7%, respectively. Total hypophysectomy still carried a failure rate of 32.5%. Failure of surgery was common (69.6%) when the surgeon did not identify any lesion at surgery.

Macroadenomas (reported in 20.7% of the patients), extrasellar extension of the tumor (14.5%), and tumor invasiveness (6.7%) as well as the location of the adenoma did not influence the outcome of surgery. Lack of histological documentation of an ACTH-secreting adenoma was more frequent in patients not in remission (47.1% vs. 16.6%; $P < 0.001$).

Evidence for an underlying misdiagnosed ectopic ACTH syndrome in the group not in remission after surgery was sought by reviewing the cause of death of the patients. Five of 26 patients died of cancer (metastatic tumor of unknown origin, uterine carcinoma, ovarian cancer, breast cancer, and metastatic carcinoid) 2, 10, 27, 42, and 57 months after operation, respectively. In 2 additional patients, a clinical suspicion of ectopic syndrome was reported. Thus, misdiagnosis of ectopic ACTH-syndrome seems to be a possible explanation for the therapeutic failure in a small subgroup of patients.

Recurrences

The analysis of the recurrences included the 510 patients who were considered in remission after operation. One hun-

