Acta Neurochir (Wien) (2004) 146: 27–35
DOI 10.1007/s00701-003-0174-3

Acta Neurochirurgica
Printed in Austria

Clinical Article

Impact of primary surgery on pituitary function in patients with non-functioning pituitary adenomas – a study on 721 patients

P. Nomikos[1], **C. Ladar**[1], **R. Fahlbusch**[2], and **M. Buchfelder**[1]

[1] Department of Neurosurgery, University of Erlangen-Nürnberg, Erlangen, Germany
[2] Department of Neurosurgery, University of Göttingen, Göttingen, Germany

Published online January 7, 2004

Summary

Introduction. The aim of this study was to define the impact of surgery on pituitary function in a large consecutive series of patients harbouring non-functioning pituitary adenomas.

Materials and method. Between December 1982 and December 2000, a total of 822 patients underwent primary surgery in the authors' department. In 721 cases a complete set of endocrinological data was available. Functions of the pituitary-gonadal, pituitary-thyroid and pituitary-adrenal axes were assessed immediately before surgery and again one week, 3 months and 1 year after the operation, utilizing standardized tests and commercially available assays.

Results. There was some degree of pre-operative hypopituitarism in 561 (85%) and 53 (86.3%) of the patients belonging to the transsphenoidal and the transcranial groups, respectively. Prior to transsphenoidal [transcranial] surgery, 163 (31%) [34 (55.7%)] of the patients had secondary adrenal deficiency, 463 (76.6%) [49 (89%)] had hypogonadism and 105 (19.1%) [14 (25.4%)] were hypothyroid. Preoperatively, prolactin levels were mildly elevated in 167 patients (25.3%), whereas 1 year after surgery, levels were elevated in only 5 patients. Permanent diabetes insipidus occurred in 4 patients, 2 from the transsphenoidal group (0.3%) and 2 from the transcranial group (3.2%). Following transsphenoidal surgery 110 (19.6%) of patients had normal pituitary function [versus 0% after transcranial surgery], 169 (30.1%) [6 (11.3%)] showed improvement, 274 (48.9%) [49 (73.7%)] had persistent deficits and 8 (1.4%) [8 (15%)] showed deterioration of pituitary function.

Discussion. These data indicate that transsphenoidal surgery for non-functioning pituitary adenomas in expert hands is, relatively, far less detrimental to patients compared with transcranial surgery. The latter carries a much greater risk of post-operative deterioration in pituitary function.

Keywords: Non-functioning pituitary adenomas; pituitary surgery; hypopituitarism; postoperative outcome; transsphenoidal; transcranial.

Introduction

In most cases, non-functioning pituitary adenomas clinically present only after having reached a considerable size. Unless the lesions are found incidentally, they result in clinical symptoms and signs secondary to compression of adjacent anatomical structures, e.g. the pituitary, optic pathways and oculomotor nerves. In early series, visual compromise was the presenting sign in the vast majority of cases. From the early 1980's, the development of imaging techniques, such as computerized tomography (CT) and magnetic resonance imaging (MRI), and the introduction of sophisticated laboratory assessment of endocrinological function allowed much earlier detection of these lesions. Due to the decreased extension of the lesions, as a consequence of the earlier detection, the prevalence of visual disturbances in patients with non-functioning pituitary adenomas has progressively declined and hormonal deficiencies involving all axes of the hypothalamo-pituitary system gradually evolved to become the leading presenting symptoms and signs in these cases [2, 14, 27, 29, 45].

The importance of hypopituitarism is emphasised by the fact that in patients with pituitary deficits there is a clear tendency towards reduced quality of life and reduced life expectancy [8, 12, 39]. Even in patients on adequate replacement therapy, cardiovascular and cerebrovascular diseases contribute significantly to the increase of overall mortality [12, 39].

Selective adenomectomy, a term first introduced by Hardy in 1969, equates to removal of as much tumorous tissue as possible whilst preserving the surrounding normal pituitary gland and has since become the gold standard in modern pituitary surgery [25]. In this respect,

there are a considerable number of publications concerning the endocrinological outcome of hypersecretion syndromes in patients with pituitary adenomas but surprisingly few data exist on the impact of surgical intervention on post-operative pituitary function itself. Thus, the aim of this study was the evaluation and assessment of the exact degree of hypopituitarism before and after primary surgery in a large consecutive series of patients harbouring non-functioning pituitary adenomas treated by a group of experienced pituitary surgeons using standardized modern operative techniques. In addition, the outcome in patients receiving transsphenoidal and transcranial surgery has been compared to help determine if there is a difference, in terms of post-operative pituitary function, between the two approaches.

Patients and methods

Patient selection

Between December 1982 and December 2000, a total of 1179 consecutive operations (1027 transsphenoidal and 152 transcranial) were performed on patients harbouring non-functioning pituitary adenomas in the Department of Neurosurgery of the University of Erlangen-Nürnberg. Of these, 822 patients (454 males and 368 females) underwent primary surgery (750 transsphenoidal, 72 transcranial) and data from these are the basis of the present study. The age at diagnosis ranged from 11 to 84 years. Twelve patients were younger than 20 years. The mean ($\pm$SD) age for all patients was 54.2 $\pm$ 19 years.

Pituitary endocrine function was assessed preoperatively and on day 7 post surgery. Complete pre- and postoperative data were available in 819 patients. Further assessments were performed 3 and 12 months post surgery, on 783 and 721 patients respectively. For the remaining patients, mostly referred from abroad, reliable endocrinological follow-up data was not available. Therefore, the endocrinological evaluation herein reported concerns only patients for whom the results of the endocrinological evaluation were available pre-operatively and at 7 days and 12 months after surgery (a total of 721 patients, 401 males and 320 females) corresponding to 87.7% of the primary surgery group. The transsphenoidal and transcranial approaches were used in 660 and 61 cases, respectively. The operative techniques have been previously described [20, 23]. During surgery in all cases, an attempt was made to resect the neoplastic tissues completely and selectively. Compete tumour removal, based on neuroradiological assessment at 3 months after surgery (demonstrating a classical ''empty sella'') was achieved in 416 (62.9%) and 27 (44.2%) of the transsphenoidally and transcranially ''operated'' patients, respectively. Sixty five patients received postoperative external radiation therapy for residual invasive tumour remnants 4–15 months (mean 6.3 $\pm$ 2.2) after surgery.

Endocrinological evaluation

Anterior pituitary function

For evaluation of anterior pituitary function, dynamic stimulation was performed with an intravenous bolus injection of 250 µg synthetic adrenocorticotropic hormone ($ACTH_{1-24}$) (Synacthen®, Ciba-Geigy, Wehr, Germany), 200 µg thyrotropin-releasing hormone (Relefact®, Hoechst, Bad Soden, Germany) and 100 µg gonadotropin-releasing hormone (Relefact LH-RH®, Hoechst). Since March 1996 stimulation was performed only by injection of ACTH. Basal and stimulated (30-minute) cortisol, and basal thyroid-stimulating hormone, luteinizing hormone and follicle-stimulating hormone were measured in the serum, as well as the basal levels of prolactin, growth hormone, total (1982–1989) or free T3 and T4 (1989–2000), and also estradiol or testosterone according to the patient's gender. The basal values for hormones tested were assigned according to the manufacturers' instructions for the hormone assays used.

Hormones were measured using specific commercially available radioimmunoassays (RIAs) and enzyme linked assays (ELISAs), as follows: *cortisol*: 1982–89 RIA (Becton-Dickinson, Heidelberg, Germany), 1989–2000 ELISA (Abbott, Wiesbaden, Germany), *prolactin*: 1982–89 RIA (Behringwerke, Marburg, Germany), 1989–2000 ELISA (Behringwerke, Marburg, Germany), *gonadotropins*: 1982–89 RIA (Behringwerke, Marburg, Germany), 1989–2000 ELISA (Pharmacia & Upjohn, Erlangen, Germany), *testosterone:* 1982–89 RIA (Sorin Biomedica SpA, Saluggia, Italy), 1989–2000 ELISA (BioChem ImmunoSystems GmbH, Freiburg, Germany), *oestradiol*: 1982–89 RIA (Baxter, Merz and Dase AG, Düdingen, Germany), 1989–2000 ELISA (BioChem ImmunoSystems GmbH, Freiburg, Germany), *thyroid-stimulating hormone*: 1982–2000 RIA (Behringwerke, Marburg, Germany), *total T3 and total T4*: 1982–89 RIA (Behringwerke, Marburg, Germany), *free T3*: 1989–2000 RIA (Behringwerke, Marburg, Germany) and *free T4*: 1989–2000 RIA (Baxter-Travenol, Munich, Germany).

Posterior pituitary function

Fluid intake, urine output and serum electrolytes were closely monitored in all patients for possible disturbance of water and electrolyte balance for 8 days postoperatively. A daily urine output >2500 ml with low specific gravity and a normal serum sodium concentration was considered indicative of diabetes insipidus.

In addition to hormone evaluation by the above mentioned tests, clinical signs and symptoms of hypopituitarism were evaluated by means of a standardised questionnaire and physical examination. In premenopausal females, assessment of menstrual cycle abnormalities (e.g. oligomenorrhea or amenorrhea) and in males, loss of facial and body hair and loss of libido and potency and low basal levels of estradiol and testosterone led to the diagnosis of hypogonadism. Its pituitary origin was concluded from low basal levels of gonadotropins and/or a less than three-fold increase in luteinizing hormone and a less than two-fold increase in follicle-stimulating hormone after administration of gonadotropin-releasing hormone. In case of postmenopausal women, failure of the hypothalamo-pituitary-gonadal axes was diagnosed when the serum gonadotropins were low or low normal in the presence of low serum estrogen. Secondary adrenocortical failure was diagnosed in cases of antecedent malaise, circulatory collapse, unexplained vomiting, weight loss and insufficient stimulation of the serum cortisol levels after ACTH administration (e.g. increase in cortisol of less than 500.4 nmol/l during ACTH stimulation). Secondary hypothyroidism was associated with constant feeling of coldness, coarsening and shedding of hair, thickening of the skin and low peripheral T3 and T4 with lowered basal TSH and/or insufficient stimulation after TRH administration in the absence of severe nonthyroid illness or of replacement therapy with thyroid hormones for goitre prophylaxis. Growth hormone secretion was not systematically assessed in these patients.

Tumour size

The size of the tumour was measured on MR images or CT scans and additionally estimated intra-operatively by the surgeon by comparison with micro-instruments. A spherical volume distribution was assumed and the estimated mean diameter of the tumour was used for further calculations.

Immunohistochemistry

Adenoma tissue was investigated by immunohistochemistry, particularly to exclude prolactinomas. When gonadotropins or ACTH were

expressed by respective immunostaining, the tumours were classified as non-functioning adenomas if serum cortisol, ACTH, LH and FSH levels were normal or subnormal.

Statistical analysis

Statistical analysis of the data concerning the influence of age, tumour size and preoperative prolactin level on the degree of hypopituitarism and improvement of pituitary function was performed using the chi-square test and the Student's t test.

Results

The most common presenting symptoms and signs encountered were endocrinological disturbances followed by visual disturbances, headache and those of pituitary apoplexy (Table 1). Among all patients, clinical and endocrinological evaluation revealed evidence of some degree of hypopituitarism preoperatively in 561 (85%) of the patients operated upon via the transsphenoidal route and in 53 (86.8%) patients of the transcranial group. In the transsphenoidal group, postoperative clinical and endocrinological examination revealed impaired pituitary function in 475 (72%) patients after 3 months and in 455 (69%) patients after one year. In contrast, following primary transcranial surgery, the percentage of patients with endocrine deficits was considerably higher as follows: hypopituitarism was encountered postoperatively in 57 (94%) patients after 3 months and in 58 (95%) patients after one year. At 12 months following transsphenoidal surgery, anterior pituitary function was normalized in 110 (19.6%), improved in 169 (30.1%), remained unchanged in 274 (48.9%) and worsened in 8 (1.4%) of the 561 patients with some degree of preoperative hypopituitarism (Table 2). Endocrine deficiencies in patients with normal preoperative pituitary function occurred in 4 of 99 (4%) cases. At 12 months following transcranial surgery, anterior pituitary function was not normalized in any patient but was improved in 6 (11.3%), remained unchanged in 49 (73.7%) and worsened in 8 (15%) of the 53 patients with preoperative impairment of anterior pituitary function. In 5 of the 8 transcranially operated patients presenting without endocrine deficits, deterioration of pituitary function was encountered (Table 3).

Table 1. *Presenting symptoms of all surgically treated patients harbouring non-functioning adenomas (n = 721)*

Presenting symptoms and signs	Number of patients (%)
Endocrinological disturbances	345 (47.8%)
Visual disturbances	222 (30.8%)
Headache	70 (9.7%)
Incidental finding	57 (7.9%)
Pituitary apoplexy	27 (3.7%)

Prolactin

Of the 199 (27.6%) patients presenting with hyperprolactinemia, 36 received dopamine agonists prior to surgical treatment. In these cases, the evaluated outcome was based on PRL levels before the medical treatment with dopamine agonists.

Transsphenoidal surgery

Preoperatively, prolactin levels were elevated in 167 (25.3%) patients. This mild elevation did not exceed 3150 mU/l. Hyperprolactinemia rapidly resolved postsurgery in 135 cases after 1 week and in another 27 cases after 3 months. Furthermore, after one year hyperprolactinemia resolved in all but three cases, thus necessitating long term treatment with dopamine agonists in only two female patients in the child-bearing age.

Transcranial surgery

The majority (n = 32, 52.4%) of the patients harbouring a pituitary adenoma with marked suprasellar extension were found to have mildly elevated prolactin levels. One year following treatment, hyperprolactinemia persisted in only 6 of the cases.

Table 2. *Postoperative endocrinological outcome in patients presenting with some degree of hypopituitarism*

	Preoperative endocrine deficits	Postoperative endocrine deficits			
		Normalized	Improved	Unchanged	Worse
Transsphenoidal surgery N = 660	561 (85%)	110 (19.6%)	169 (30.1%)	274 (48.9%)	8 (1.4%)
Transcranial surgery N = 61	53 (86.8%)	0	6 (11.3%)	49 (73.7%)	8 (15%)

Table 3. *Deterioration of pituitary function in patients with normal preoperative pituitary function*

	Normal preoperative pituitary function	New postoperative endocrine deficit
Transsphenoidal surgery N = 660	99 (15%)	4 (4%)
Transcranial surgery N = 61	8 (13.2%)	5 (62.5%)

Pituitary-adrenocortical-axis

Transsphenoidal surgery

Partial (n = 163) or complete (n = 33) secondary adrenocortical failure was observed preoperatively in 196 (34.8%) of patients. 12 months after surgery adrenal deficiency was encountered in 116 of 660 (17.5%) patients, whereas by that time complete adrenocortical failure when presented preoperatively, showed almost no tendency to recover (32 of 33 cases). Of 196 patients, adrenocortical function was normalized in 80 (40.8%), improved in 61 (31.1%), unchanged in 46 (23.6%) and worsened in 9 (4.5%) cases. New deficits were found in 4 of 464 (0.8%) cases with preoperatively normal adrenocortical function.

Transcranial surgery

Secondary adrenocortical failure was observed preoperatively in 34 (55.7%) of patients and this did not completely resolve following surgery in any of the cases, although it improved in 4 cases (11.7%). Of the remaining patients, adrenocortical status remained unchanged in 22 (64.7%) and worsened in 8 (23.6%) cases. New deficits were found in 8 of 27 (29.6%) cases with normal preoperative adrenocortical function.

Pituitary-gonadal-axis

Secondary hypogonadism was the most common endocrinological failure found in these patients. The evaluation of the pituitary gonadal axis was difficult in individual cases. Six patients (4 males and 2 females) were younger than 15 years and were excluded. Of the remaining patients, hypogonadism could not be reliably excluded in 56 cases since they used oral contraceptives or were suffering from primary hypogonadism when investigated before and at 12 months after surgery. In a total of 659 patients (604 transsphenoidal, 55 transcranial) reliable data could be collected.

Transsphenoidal surgery

Hypogonadism was found in 463 (76.6%) of patients. The number of patients with hypogonadism decreased three months after surgery to 392 of 604 (64.9%) and there was no evidence of further improvement in this axis at the one year follow-up examination (n = 392). Of 463 patients, secondary hypogonadism resolved in 74 (15.9%), and remained unchanged in 389 (84.1%). New deficits were found in 3 of 141 (2.1%) cases with preoperatively normal gonadal pituitary axis.

Transcranial surgery

Secondary hypogonadism was found in 49 (89%) cases. The number of patients with hypogonadism increased three months after surgery to 52 of 55 (94.5%) and, as in patients following transsphenoidal surgery, there was no sign of further improvement in this axis at the one year follow-up examination (n = 52). Of 49 patients, secondary hypogonadism resolved in only 2 (4%), remaining unchanged in 50 (96%) cases. New deficits were found in 3 of 6 (50%) cases with normal preoperative gonadal pituitary axis.

Pituitary-thyroid-axis

Of the 660 patients in the transsphenoidal and of the 61 patients in the transcranial surgery group 57 (8.6%) and 6 (9.8%), respectively, were already receiving thyroid replacement therapy because of other thyroid disease, in most cases for endemic goitre, which is common in Bavaria and therefore had to be excluded from the following evaluation [24, 33].

Transsphenoidal surgery

Preoperatively, 115 of 603 (19.1%) patients had evidence of secondary hypothyroidism. At 12 months after surgery 82 of 603 (16.3%) were found to still suffer from secondary hypothyroidism. Of 115 patients, secondary hypothyroidism resolved in 39 (33.9%), and remained unchanged in 76 (66.1%). New deficits were found in 6 of 388 (1.5%) cases with preoperatively normal thyroid pituitary axis.

Transcranial surgery

Preoperatively 14 of 55 (25.4%) patients had evidence of secondary hypothyroidism. At 12 months after surgery, 13 of 55 (23.6%) were found to still suffer from secondary hypothyroidism. Of 14 patients, secondary

hypothyroidism resolved in 4 (28.5%), and remained unchanged in 10 (71.5%). New deficits were found in 3 of 41 (7.3%) cases with normal preoperative thyroid pituitary axis.

Diabetes insipidus

None of the 721 patients exhibited diabetes insipidus preoperatively. In 2 patients with polydipsia, diabetes insipidus was excluded by an overnight dehydration test. 4 patients (0.5%) exhibited permanent postoperative diabetes insipidus at 12 months after surgical treatment, 2 from the transsphenoidal and 2 from the transcranial surgery group. During the early postoperative period transient diabetes insipidus and/or electrolyte disturbances occurred in up to 34% of cases, a percentage which corresponds to our previous publications [11, 26].

Impact of age, tumour size and preoperative prolactin levels on degree of pre- and postoperative pituitary function

Age

Patients' age at surgery was compared with the degree of preoperative hypopituitarism and the recovery of pituitary function by dividing the patients into four groups (Table 4). No correlation could be found between these parameters.

Tumour size

Tumour size was compared with the degree of preoperative hypopituitarism and the recovery of pituitary function by categorizing the patients into 5 groups ranging from <10 to >40 mm (Table 5). The degree of preoperative hypopituitarism was found to be significantly lower ($P<0.01$) and the recoveries of pituitary function significantly higher in patients with smaller tumours ($P<0.001$). The mean tumour size in patients with improvement or normalization of pituitary function was found to be 26 ± 6 mm and was significantly less than in patients with persistent impairment of pituitary function (33 ± 9 mm, $P<0.001$).

Table 4. *Rates of preoperative hypopituitarism and partial or complete recovery of pituitary function in different age groups*

Age at surgery	Number of patients (n)	Preoperative hypopituitarism	Partial or complete recovery of pituitary function following surgery
12–20 years	73	58 (79.4%)	16 (27.5%)
20–40 years	244	212 (86.8%)	50 (23.5%)
40–60 years	300	254 (84.6%)	63 (24.8%)
60–84 years	104	90 (86.5%)	20 (22.2%)

Table 5. *Preoperative hypopituitarism and recovery of pituitary function depending on tumour size*

Tumour size	Number of patients (n)	Preoperative hypopituitarism	Partial or complete recovery of pituitary function following surgery
>10 mm	22	16 (72.7%)	14 (87.5%)
10–20 mm	221	157 (71%)	114 (72.6%)
20–30 mm	334	298 (89.2%)	164 (55%)
30–40 mm	106	103 (97.1%)	25 (24.2%)
>40 mm	38	38 (100%)	4 (10.5%)

Table 6. *Preoperative hypopituitarism and recovery of pituitary function as related to pretreatment prolactin levels*

Preoperative prolactin levels	Preoperative hypopituitarism	Partial or complete recovery of pituitary function following surgery
<100 µU/ml, n = 154	113 (73.3%)	34 (30%)
100–500 µU/ml, n = 368	313 (85%)	164 (52.3%)
>500 µU/ml, n = 199	195 (97.9%)	156 (80%)

Prolactin levels

Preoperative prolactin levels were found to be low (4–100 mU/l) in 154 (21.3%) patients. In 368 (51%) patients, prolactin levels ranged between 101–500 mU/l. As described above, 199 (27.7%) patients presented with mild hyperprolactinemia. The rate of partial or complete recovery of the pituitary function was found to be significantly higher in patients with elevated preoperative prolactin levels ($p<0.001$), while only 34 of 113 (30%) patients with hypopituitarism and initial prolactin levels below 100 mU/l showed improvement of pituitary function (Table 6).

Discussion

Results

Postoperative pituitary deficiency, particularly panhypopituitarism, is considered a significant complication of pituitary surgery because it dramatically affects the patient's quality of life by necessitating hormonal substitution therapy. Following the introduction of

Table 7. *Impact of surgery on preoperatively impaired pituitary function in patients harbouring nonfunctioning pituitary adenomas*

Author year of publication	No. of patients total/ endocrine deficiency	Surgical approach*	Improvement n (%)	No change n (%)	Deterioration n (%)
McLanachan *et al.* 1978 [32]	40/17	Ts	10 (58.8%)	4 (23.5%)	3 (17.7%)
Nelson *et al.* 1984 [35]	84/28	Ts	10 (35.7%)	9 (32.1%)	9 (32.1%)
Arafah *et al.* 1986 [3]	26/26	Ts	17 (65.3%)	8 (30.7%)	1 (4%)
Arafah *et al.* 1990 [5]	8/8 (pit. apoplexy)	Ts	5 (62.5%)	3 (37.5%)	
Marazuela *et al.* 1994 [30]	35/24	Ts	11 (45.8%)	13 (54.2%)	
Webb *et al.* 1999 [44]	234/93	Ts	45 (48%)		
This series	660/561	Ts	279 (49.7%)	274 (48.9%)	8 (1.4%)
	61/53	Tc	6 (11.3%)	49 (73.7%)	8 (15%)

transsphenoidal microsurgery in the management of patients with pituitary tumours, selective adenomectomy has become the main aim in order to preserve as much normal pituitary tissue as possible. Several studies demonstrated that preservation of pituitary tissue was mostly associated with no further loss of pituitary function. However, earlier studies examined only the incidence of deterioration in pituitary function following surgery. It is only recently reported, by several groups, that impaired pituitary function could actually be restored by selective surgical resection of the adenomas (Table 7) [4, 5, 32, 35, 38]. This observation is confirmed by the present study in which a large patient cohort was homogeneously assessed, treated by the same surgical techniques and evaluated in one laboratory. Residual anterior pituitary function was more frequently preserved after transsphenoidal surgery (54%) and could even be normalized or improved in 40% of cases. In contrast to most reports in the literature, only a moderate increase in anterior pituitary deficiency was observed as an untoward effect of the operation. Importantly, the incidence of this deterioration was significantly higher in those patients undergoing transcranial surgery.

Recovery of anterior pituitary function after surgery in non-functioning adenomas has not been adequately appreciated in the past. The reported rate of postoperative secondary adrenal insufficiency is found in the range of 30% and 62% [37, 40, 42, 43]. Compared to these figures, the patients in our series (37%) did slightly better. Concerning gonadal dysfunction, there is a general agreement, that this axis is the most often involved, apart from the GH-axis [17, 30, 44]. Although Turner *et al.* found a relatively low preoperative rate of only 21% in a series of 65 patients, it should be considered that low serum gonadotropins were the key factor in making the diagnosis [42]. However, clinical aspects, such as loss of libido or oligomenorrhea, were not considered. Marzuela *et al.* found a preoperatively deficient thyroid axis in 23% of cases. Postoperatively, this percentage was almost unchanged at about 20%. Turner *et al.* reported a similar rate of postoperative thyroid insufficiency (24%). These results approximately concur with those of the present series. In contrast, Van Lindert *et al.* observed an increase in secondary hypothyroidism after transcranial surgery from 21% preoperatively to 56% postoperatively comparable to the results of the present evaluation [43].

In the present series, symptoms and signs related to endocrine deficiency were one of the most common presenting problems found in patients harbouring a non-functioning pituitary adenoma (47.8%), and therefore often prompted medical consultation. The only other major initial sign was visual compromise (30.8%). In agreement with other previous studies these signs relate to tumour mass effect, reflecting chiasmal and pituitary stalk compression [17, 30]. Most of these tumours occurred in middle aged patients, with a maximum between 51 and 60 years. Secondary hypogonadism could be seen in most cases (77%) and these data correlate with previous publications [17]. Our data confirm the ''conventional'' order of appearance of target gland failure, since partial adrenal deficiency was diagnosed more frequently (49%) than hypothyroidism (18.4%).

The results achieved 3 months after surgery predicted the long-term outcome. There was no striking further improvement one year later, particularly in the corticotropic and gonadal function.

Endocrine results were clearly dependent on the type of surgery, in terms of both anterior pituitary function and diabetes insipidus. After transcranial surgery, permanent diabetes insipidus was observed in 10% of patients by Van Lindert, whereas in the presented cohort just 3.4% of the patients exhibited permanent postoperative diabetes insipidus [43]. In contrast, the rate of diabetes insipidus following transsphenoidal surgery was found to be very low (0.3%) as reported by other expert pituitary surgeons [11].

Methods

The combined ACTH-TRH-LRH-test used until 1996 was abandoned in our service, when one patient with a non-functioning macro-adenoma became amaurotic minutes after injection of the test substances. Results of similar cases have been published [15, 19, 31]. Therefore, since 1996 endocrine function was assessed by measuring only cortisol levels during a short ACTH-Test, by determination of all other basal pituitary hormones and the evaluation of clinical signs and symptoms of hypopituitarism by means of a standardized questionnaire and physical examination. The main disadvantage of this procedure is that there is no information on the integrity of the growth hormone axis and only indirect information on the hypothalamo-pituitary-adrenal (HPA) axis can be obtained. However, concerning the HPA axis, it has been demonstrated that the results closely correlate to those of an insulin tolerance test or a corticotropin-releasing hormone stimulation test unless acute dramatic changes occur [1, 13, 16, 34, 36, 41]. ACTH-stimulation in combination with the determination of basal levels of all other pituitary hormones and knowledge of the clinical condition of the patient proved to be a rational, less time-consuming alternative to the insulin tolerance test [22, 28].

The necessity of replacement therapy was also taken into consideration: for the evaluation of the pituitary-adrenal axis in preoperatively deficient patients. The terms 'resolution of deficiency' and 'improved', 'unchanged' or 'worse pituitary function' were used depending on the postoperative endocrinological evaluation and the dose of replacement therapy needed. However, for the evaluation of the impact of surgery on the gonadal axis in patients with preoperative secondary hypogonadism, only the terms 'resolution of deficiency' and 'unchanged pituitary function' were used, since there is no benefit for the hypogonadal patients when gonadotropins are improved but still subnormal after surgical treatment. For the evaluation of the impact of surgery on the pituitary-thyroid axis in preoperatively deficient patients, the terms 'resolution of deficiency' and 'unchanged pituitary function' were used depending on the postoperative endocrinological evaluation and the necessity of replacement therapy, since there is again no benefit for the deficient patient when postoperative thyroid hormones are improved but still subnormal. Since replacement therapy is still necessary in such cases, it makes no practical difference which dose a single tablet contains. Thus, even in cases of improvement, the continuing abnormal gonadal and thyroid functions were characterized as clinically unchanged after surgery if replacement therapy was necessary.

Factors influencing the endocrinological outcome

Several investigators reported mild hyperprolactinemia accompanying hypopituitarism associated with pituitary macro-adenomas not secreting PRL as a presenting feature of non-functioning pituitary adenoma. Whilst Marazuela *et al.* report 48% of patients with preoperative hyperprolactinemia, Comtois *et al.* mention a higher incidence of 65% [17, 30]. In the present series, the percentage of abnormally elevated plasma PRL was found to be lower, namely 19% (167 out of 882 patients). Serum PRL levels never exceeded 3150 mU/l. It is generally accepted that hyperprolactinemia associated with non-functioning pituitary adenomas results from the compression of the pituitary stalk with consequent reduction of prolactin inhibiting factor delivery. Despite hyperprolactinemia, a dopamine agonistic therapy does not reliably induce regression of these adenomas, in contrast to that found with prolactinomas [9, 10].

Previous studies indicated preoperative prolactin levels were a useful predictor of postoperative recovery of pituitary function [7]. We observed that in patients who had mildly elevated prolactin levels prior to surgery, pituitary function was more likely to recover. In agreement with previous reports [3, 6, 30], these data suggest that the mechanism causing hypopituitarism in large pituitary adenomas, may be infundibular compression and the resulting impaired delivery of hypothalamic hormones, rather than destruction of the pituitary tissue by the tumour. This explains the better recovery rate of pituitary function in cases with preoperative hyperprolactinemia.

A correlation could be demonstrated between tumour size and elevation of prolactin levels. The highest rates of preoperative hyperprolactinemia clearly occurred in the group with a tumour size between 20 and 30 mm. It

is postulated that further invasive expansion of tumours into the supra- and parasellar space might lead to destruction of the pituitary gland and therefore reverse hyperprolactinemia. Tumour size also influenced the rate of gonadal deficiency. The "critical" tumour size was found to be about 20 mm, with 87% of patients having signs of hypogonadism. In contrast only 57% of patients with a tumour size of 30 mm had evidence of hypogonadism. This was a similar finding compared to the correlation between tumour size and hypocortisolism rate. Hormone deficiency rates tended to increase in number with advancing age. A grossly concurrent development was observed with respect to gonadal dysfunction. Still these findings should be interpreted with caution, because there is evidence of hypogonadism occurring with advancing age in any population.

Transsphenoidal versus transcranial surgery

The introduction by Cushing of the transsphenoidal approach to removal of pituitary adenomas dramatically improved patient survival and this method is now considered the first choice surgical treatment [18, 21]. Nevertheless, in a small percentage of cases, the transsphenoidal approach is not a suitable option. Contra-indications to the transsphenoidal approach include a sphenoid sinus which shows no sign of pneumatisation, and a tumour which is mainly extrasellar [23]. In such cases, the transcranial approach is indicated and, although only a small percentage of patients require this type of surgery, a significant number are involved in any neurosurgical centre. Thus, it is imperative to fully understand and decipher the outcomes of the transcranial route, especially in comparison with the transsphenoidal route. For this reason, we have compared the incidence of post-operative pituitary dysfunction or recovery in groups of patients undergoing both types of surgery.

The results clearly demonstrate a greatly increased incidence of poorer prognosis, in terms of pituitary function, in the transcranial patients. This might reflect that the characteristics of the adenomas in this group of patients are, in some way, associated with more difficult selective adenomectomy. Alternatively, the poorer prognosis may be an inherent problem with the transcranial approach. The present results further show that the transsphenoidal route should be used whenever possible in order to reduce the risk of post-operative complications.

Conclusions

It has been demonstrated that in expert surgical hands, normal anterior pituitary function is usually maintained and often improved following surgery of non-functioning pituitary adenomas. These results strengthen the indication for surgery in patients with hypopituitarism but no visual compromise. This observation applies particularly to the transsphenoidal approach, and in a lesser way to transcranial surgery. Data indicated that deterioration of pituitary function following transsphenoidal surgery is rare. However, care should be taken not to generalize these results, which are less likely be reproduced by surgeons with limited experience in pituitary surgery. Supraregional specialization in a few neurosurgical centres which closely cooperate with endocrinologists may lead to even better surgical results concerning the preservation and restoration of pituitary function following surgery.

References

1. Abdu TA, Elhadd TA, Neary R, Clayton RN (1999) Comparison of the low dose short synacthen test (1 microg), the conventional dose short synacthen test (250 microg), and the insulin tolerance test for assessment of the hypothalamo-pituitary-adrenal axis in patients with pituitary disease. J Clin Endocrinol Metab 84: 838–843
2. Anderson D, Faber P, Marcovitz S, Hardy J, Lorenzetti D (1983) Pituitary tumors and the ophthalmologist. Ophthalmology 90: 1265–1270
3. Arafah BM (1986) Reversible hypopituitarism in patients with large nonfunctioning pituitary adenomas. J Clin Endocrinol Metab 62: 1173–1179
4. Arafah BM, Brodkey JS, Manni A, Velasco ME, Kaufman B, Pearson OH (1982) Recovery of pituitary function following surgical removal of large nonfunctioning pituitary adenomas. Clin Endocrinol (Oxf) 17: 213–222
5. Arafah BM, Harrington JF, Madhoun ZT, Selman WR (1990) Improvement of pituitary function after surgical decompression for pituitary tumor apoplexy. J Clin Endocrinol Metab 71: 323–328
6. Arafah BM, Kailani SH, Nekl KE, Gold RS, Selman WR (1994) Immediate recovery of pituitary function after transsphenoidal resection of pituitary macroadenomas. J Clin Endocrinol Metab 79: 348–384
7. Arafah BM, Nekl KE, Gold RS, Selman WR (1995) Dynamics of prolactin secretion in patients with hypopituitarism and pituitary macroadenomas. J Clin Endocrinol Metab 80: 3507–3512
8. Bates AS, Bullivant B, Sheppard MC, Stewart PM (1999) Life expectancy following surgery for pituitary tumours. Clin Endocrinol (Oxf) 50: 315–319
9 Bevan JS, Burke CW (1986) Non-functioning pituitary adenomas do not regress during bromocriptine therapy but possess membrane-bound dopamine receptors which bind bromocriptine. Clin Endocrinol (Oxf) 25: 561–572
10. Bevan JS, Webster J, Burke CW, Scanlon MF (1992) Dopamine agonists and pituitary tumor shrinkage. Endocr Rev 13: 220–240
11. Boehnert M, Hensen J, Henig A, Fahlbusch R, Gross P, Buchfelder M (1998) Severe hyponatremia after transsphenoidal surgery for pituitary adenomas. Kidney Int [Suppl] 64: S12–14
12. Bulow B, Hagmar L, Mikoczy Z, Nordstrom CH, Erfurth EM (1997) Increased cerebrovascular mortality in patients with hypopituitarism. Clin Endocrinol (Oxf) 46: 75–81
13. Burke CW (1992) The pituitary megatest: outdated? Clin Endocrinol (Oxf) 36: 133–134

14. Chamblin M, Davidoff LM (1955) Ophthalmological changes produced by pituitary tumors. Am J Ophthalmol 40: 353–368
15. Cimino A, Corsini R, Radaeli E, Bollati A, Giustina G (1981) Transient amaurosis in patient with pituitary macroadenoma after intravenous gonadotropin and thyrotropin releasing hormones. Lancet 2: 95
16. Cohen R, Bouquier D, Biot-Laporte S, Vermeulen E, Claustrat B, Cherpin MH, Cabrera P, Guidetti P, Ferry S, Bizollon CA *et al* (1986) Pituitary stimulation by combined administration of four hypothalamic releasing hormones in normal men and patients. J Clin Endocrinol Metab 62: 892–898
17. Comtois R, Beauregard H, Somma M, Serri O, Aris-Jilwan N, Hardy J (1991) The clinical and endocrine outcome to transsphenoidal microsurgery of nonsecreting pituitary adenomas. Cancer 68: 860–866
18. Cushing H (1914) The Weir Mitchell lecture: Surgical experiences with pituitary disorders. JAMA 63: 1515–1525
19. Drury PL, Belchetz PE, McDonald WI, Thomas DG, Besser GM (1982) Transient amaurosis and headache after thyrotropin releasing hormone. Lancet 1: 218–219
20. Fahlbusch R, Buchfelder M (1988) Transsphenoidal surgery of parasellar pituitary adenomas. Acta Neurochir (Wien) 92: 93–99
21. Fahlbusch R, Buchfelder M (1996) Surgical complications. In: Landolt AM, Vance ML, Reilly PL (eds) Pituitary adenomas. Churchill Livingstone, New York, pp 395–408
22. Fahlbusch R, Buchfelder M (2000) Tests of endocrine function for neurosurgical patients. In: Crockard A, Hayward R, Hoff J (eds) Neurosurgery: the scientific basis of clinical praxis. Blackwell Science, Oxford, pp 935–945
23. Fahlbusch R, Honegger J, Buchfelder M (1993) Surgical therapy of tumors in the area of the sella, clivus and cavernous sinus. Eur Arch Otorhinolaryngol [Suppl] 1: 205–217
24. Hampel R, Kulberg T, Klein K, Jerichow JU, Pichmann EG, Clausen V, Schmidt I (1995) [Goiter incidence in Germany is greater than previously suspected]. Med Klin 90: 324–329
25. Hardy J (1969) Transphenoidal microsurgery of the normal and pathological pituitary. Clin Neurosurg 16: 185–217
26. Hensen J, Henig A, Fahlbusch R, Meyer M, Boehnert M, Buchfelder M (1999) Prevalence, predictors and patterns of postoperative polyuria and hyponatraemia in the immediate course after transsphenoidal surgery for pituitary adenomas. Clin Endocrinol (Oxf) 50: 431–439
27. Hollenhorst RW, Younge RB (1973) Ocular manifestations produced by adenomas off the pituitary gland: analysis of 1000 cases. In: Kohler PO, Ross GT (eds) Diagnosis and treatment of pituitary tumors. Excerpta Medica, Amsterdam, pp 53–68
28. Hurel SJ, Thompson CJ, Watson MJ, Harris MM, Baylis PH, Kendall-Taylor P (1996) The short Synacthen and insulin stress tests in the assessment of the hypothalamic-pituitary-adrenal axis. Clin Endocrinol (Oxf) 44: 141–146
29. Klauber A, Rasmussen P, Lindholm J (1978) Pituitary adenoma and visual function. The prognostic value of clinical, ophthalmological and neuroradiologic findings in 51 patients subjected to operation. Acta Ophthalmol (Copenh) 56: 252–263
30. Marazuela M, Astigarraga B, Vicente A, Estrada J, Cuerda C, Garcia-Uria J, Lucas T (1994) Recovery of visual and endocrine function following transsphenoidal surgery of large nonfunctioning pituitary adenomas. J Endocrinol Invest 17: 703–707
31. Masson EA, Atkin SL, Diver M, White MC (1993) Pituitary apoplexy and sudden blindness following the administration of gonadotrophin releasing hormone. Clin Endocrinol (Oxf) 38: 109–110
32. McLanahan CS, Christy JH, Tindall GT (1978) Anterior pituitary function before and after trans-sphenoidal microsurgical resection of pituitary tumors. Neurosurgery 3: 142–145
33. Meng W, Schindler A (1997) [Nutritional iodine supply in Germany. Results of preventive measures]. Z Arztl Fortbild Qualitatssich 91: 751–756
34. Mukherjee JJ, de Castro JJ, Kaltsas G, Afshar F, Grossman AB, Wass JA, Besser GM (1997) A comparison of the insulin tolerance/glucagon test with the short ACTH stimulation test in the assessment of the hypothalamo-pituitary-adrenal axis in the early post-operative period after hypophysectomy. Clin Endocrinol (Oxf) 47: 51–60
35. Nelson AT Jr, Tucker HS Jr, Becker DP (1984) Residual anterior pituitary function following transsphenoidal resection of pituitary macroadenomas. J Neurosurg 61: 577–580
36. Oelkers W (1999) Comment on comparison of the low dose short synacthen test (1 microg), the conventional dose short synacthen test (250 microg), and the insulin tolerance test for assessment of the hypothalamo-pituitary-adrenal axis in patients with pituitary disease. J Clin Endocrinol Metab 84: 2973–2974
37. Pichl J, Buchfelder M, Mari I, Marienhagen J, Fahlbusch R (1990) Hypophysenfunktion bei Patienten mit Hypophysenadenomen. Akt Endokr Stoffw 11: 2–5
38. Popp G, Stracke H, Hildebrandt G, Schatz H (1988) Studies on the influence of selective adenomectomy on hormone secretion from normal anterior pituitary gland. Pathol Res Pract 183: 540–545
39. Rosen T, Bengtsson BA (1990) Premature mortality due to cardiovascular disease in hypopituitarism. Lancet 336: 285–288
40. Sheline G (1981) Pituitary tumors. In: Beardwell CG, Robertson GL (eds) The pituitary. Butterworth, London, pp 106–139
41. Stewart PM, Corrie J, Seckl JR, Edwards CR, Padfield PL (1988) A rational approach for assessing the hypothalamo-pituitary-adrenal axis. Lancet 1: 1208–1210
42. Turner HE, Stratton IM, Byrne JV, Adams CB, Wass JA (1999) Audit of selected patients with nonfunctioning pituitary adenomas treated without irradiation – a follow-up study. Clin Endocrinol (Oxf) 51: 281–284
43. van Lindert EJ, Grotenhuis JA, Meijer E (1991) Results of follow-up after removal of non-functioning pituitary adenomas by transcranial surgery. Br J Neurosurg 5: 129–133
44. Webb SM, Rigla M, Wagner A, Oliver B, Bartumeus F (1999) Recovery of hypopituitarism after neurosurgical treatment of pituitary adenomas. J Clin Endocrinol Metab 84: 3696–3700
45. Wray SH (1976) Neuro-ophthalmological manifestations of pituitary and parasellar lesions. Clin Neurosurg 24: 86–117

Correspondence: Panos Nomikos M.D., Department of Neurosurgery, University of Göttingen, Robert-Koch-Str. 40, D-37075 Göttingen, Germany. e-mail: nomikos@med.uni-goettingen.de