Hypopituitarism : clinical assessment in different conditions

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Chapter 5

Low incidence of adrenal insufficiency after transsphenoidal surgery in patients with acromegaly: a long-term follow-up study

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Abstract

Context: The long-term prevalence of adrenal insufficiency after transsphenoidal surgery for GH secreting pituitary adenomas is unknown. However, recently a single study reported a high prevalence of adrenal insufficiency in acromegalic patients after surgical and/or medical treatment without postoperative radiotherapy.

Objective: The objective of the study was to assess the prevalence and incidence rates of adrenal insufficiency in consecutive patients during long-term follow-up after successful transsphenoidal surgery for acromegaly.

Design: In 91 consecutive patients in remission after transsphenoidal surgery only, we retrospectively reviewed insulin tolerance tests, CRH stimulation tests, metyrapone tests, and ACTH stimulation tests used to assess corticotrope function.

Results: Early postoperatively, insufficient adrenal function was observed in 16 patients (18%), which was transient in eight and irreversible in eight other patients in the first year of postoperative follow-up. Therefore, after the first year, the prevalence of adrenal insufficiency was 9%. Late, new-onset adrenal insufficiency developed in only three patients 13, 18, and 24 yr after surgery. The incidence rate of late adrenal insufficiency after successful surgery was 2/1000 person-years. After long-term follow-up, a median of 8.1 (1–31 yr), the prevalence of secondary adrenal insufficiency was 12% in patients in remission after surgery for acromegaly.

Conclusion: The prevalence of adrenal insufficiency 1 yr after surgery was 9%, whereas during prolonged follow-up, the incidence rate of adrenal insufficiency was only 2/1000 person-years in patients in remission after surgery. Therefore, development of late-onset adrenal insufficiency is a very infrequent complication in patients with acromegaly in remission after transsphenoidal surgery only.

Introduction

Acromegaly is a chronic disabling disease caused by a GH-producing pituitary adenoma. Transsphenoidal surgery is the curative treatment of choice and somatostatin analogs or radiotherapy is given as needed (1). Hypopituitarism, requiring replacement therapy, can be present postoperatively as a result of surgical or additional radiotherapy. Pituitary irradiation induces hypopituitarism in 50%–75% of the patients after 10–20 yr of follow-up (2). The prevalence of late-onset hypopituitarism in surgically treated patients is not precisely known, but it is generally considered to occur infrequently. The 2009 guidelines on management of acromegaly state that pituitary function should be assessed three months after surgery and that if a dynamic evaluation reveals normal function, there is no need for repeated dynamic function tests unless a patient receives radiotherapy or has clinical symptoms of hypopituitarism (1). Recently, however, Ronchi *et al.* (3) evaluated adrenal function using the low-dose 1 μg ACTH stimulation test in 36 patients with acromegaly treated by surgery with or without somatostatin analog treatment or by primary medical treatment with somatostatin analogs. A cut-off value for cortisol of 500 nmol/L was used to demonstrate normal adrenal function. They reported a high prevalence of adrenal insufficiency in 32% of patients after a median duration of follow-up of 6 yr after surgery and eventually somatostatin analog treatment. The authors concluded that hypothalamic-pituitary-adrenal (HPA) axis function may worsen over time and should be carefully monitored by dynamic testing in all acromegalic patients, independently from the type of treatment. This recommendation has obvious implications for the long-term management of nonirradiated patients with acromegaly (3). However, the high prevalence of HPA axis insufficiency in surgically treated acromegalic patients is not yet confirmed by others. Therefore, the aim of the present study was to evaluate the prevalence of adrenal insufficiency during long-term follow-up in an unselected cohort of consecutive patients in remission of GH excess by transsphenoidal surgery in our hospital during the period of 1979–2003.

Patients and Methods

Patients

For this study, all 164 consecutive patients, diagnosed with acromegaly and treated at the Leiden University Medical Center, a tertiary referral center, by transsphenoidal surgery between 1979 and 2003 were reviewed. For the purpose of this study, we excluded patients, who were additionally treated by radiotherapy (n=59) as well as patients who had persistent active disease after surgery (n=14). Consequently, 91 patients were included. The diagnosis of acromegaly was based on clinical characteristics and confirmed by insufficient suppression of GH levels after an oral glucose tolerance test. All patients had careful preoperative and postoperative biochemical evaluation. Criteria for cure were serum GH less than 2.5 μg/L, normal glucose-suppressed GH levels (<1.25 μg/L for the RIA and <0.38 μg/L for the immunofluorometric assay), and normal IGF-I values for age. During postoperative follow-up, serum GH, glucose-suppressed GH levels, and IGF-I values were measured at yearly intervals. The surgical results of the complete cohort have been reported previously (4). Data regarding clinical and biochemical characteristics, treatment, and pituitary function were available from all patients. HPA axis function was routinely studied early postoperatively (7–10 days postoperatively), using the CRH test or the insulin tolerance test (ITT). Thereafter nonstimulated morning cortisol measurements were performed at yearly follow-up visits, and dynamic tests to assess corticotrope function were performed at increasing nonstandardized follow-up intervals. The Medical Ethical Committee approved the analysis of treatment results in patients with acromegaly, and no informed consent was required for this retrospective analysis.

Methods

We retrospectively evaluated HPA axis function in the total, unselected cohort of patients in remission after surgery to exclude a potential selection bias. None of the patients received pharmacological treatment

for acromegaly. We reviewed all available dynamic tests in our database performed to evaluate corticotrope function. We considered the ITT as the gold standard test. If ITT results were not available, other stimulation tests like the CRH, ACTH, and metyrapone tests were evaluated. In addition, basal morning cortisol values were collected. Patients were considered to have adrenal insufficiency if they had biochemically confirmed insufficiency (see below). All patients had an endocrine assessment every year. The use of hormone stimulation tests changed during the follow-up period. Initially, ITT was used early postoperatively and during follow-up. After the clinical introduction of the CRH and GHRH test, the ITT lost its leading position in the screening for somatotrope and corticotrope deficiencies for obvious reasons. From 1990 onward, according to protocol, the CRH test was performed early postoperatively to assess whether corticotrope function was sufficient to discharge patients without hydrocortisone replacement, and confirmation tests were performed at the outpatient department.

The metyrapone test was used for follow-up assessment in patients with contraindication for ITT. In recent years, 1 μg ACTH tests were performed to screen for corticotrope deficiency in late follow-up. However, the ITT remained the gold standard for confirmation of adrenal insufficiency, especially if other test revealed borderline results (in patients without a contraindication for ITT).

Evaluation of HPA axis

An insulin tolerance test (insulin 0.1 IE/kg, Actrapid; Novo Nordisk, Bagsvaerd, Denmark) was administered i.v. in the postabsorptive state between 0800 and 0900 h to induce hypoglycemia (< 2.2 mmol/L). Cortisol was measured at -15, 0, 15, 30, 45, 60, 90, and 120 min. A cut-off value of cortisol greater than 550 nmol/L was used to define normal function of the HPA axis (5–9). An ACTH stimulation test (ACTH 1μg Synacthen®; Novartis Pharma B.V., Arnhem, The Netherlands) was administered i.v. between 0800 and 0900 h after blood samples had been taken at -15 and 0 min for measurement of cortisol values. The response of cortisol to ACTH was assessed in a single blood sample obtained 30 min after ACTH injection. A cut-off value of cortisol greater than 550 nmol/L was used to define normal adrenal function (10–12).

CRH test (CRH 100 μg; Ferring B.V., Hoofddorp, The Netherlands) was administered in the postabsorptive state between 0800 and 0900 h.

Cortisol and ACTH were measured at -15, -5, 15, 30, 45, and 60 min. A cut-off value for cortisol of greater than 550 nmol/Liter was used to define normal function (13, 14). A Metyrapone test (metyrapone 30 mg/kg, Metopiron; Novartis Pharma B.V., Arnhem, The Netherlands) was administered at midnight. The next morning postabsorptive blood samples were obtained for measurement of 11-deoxycortisol, cortisol, and ACTH levels. A cut-off value for 11-deoxycortisol of 200 nmol/L was used to define normal adrenal function (15–17).

For morning cortisol, blood was sampled between 0800 and 0900 h for assessment of cortisol values. A cut-off value of cortisol greater than 500 nmol/L was used to define normal function only in case dynamic tests were not available. Premenopausal women were tested after stopping estrogen replacement for 3 months.

Assays

Cortisol was measured between 1978 and 1986 by in-house RIA with an interassay coefficient of variation (CV) of 10% and with a detection limit of 5 nmol/L. Between 1986 and 1994, cortisol was measured by fluorescence energy-transfer immunoassay (Syva-Advance; Syva Co., Palo Alto, CA) with an interassay variation coefficient of 3.6–6.1% and a detection limit of 0.05 μmol/L. From 1994, cortisol was measured by fluorescence polarization assay on a TDx (Abbott Laboratories, Abbott Park, IL). The interassay variation coefficient is 5–6% above 0.50 μmol/L and amounts to 12% under 20 nmol/L. The detection limit was 2 nmol/L. Before 1993 GH was measured by RIA (Biolab; Serona, Coissins, Switzerland), calibrated against World Health Organization international reference preparation 66/21 (detection limit: 0.5 mU/L, with an interassay CV less than 5%; for the conversion of micrograms per liter to milliunits per liter, multiply by 2). After 1993 serum GH concentration was measured with a sensitive time-resolved fluoroimmunoassay (Wallac, Turku, Finland). The assay is specific for 22 kDa GH. The standard was recombinant human GH (Genotropin; Pharmacia & Upjohn, Uppsala, Sweden), which was calibrated against the World Health Organization First International Reference Preparation 80/505 (to convert milliunits per liter to micrograms per liter, divide by 2.6) (18). The limit of detection (defined as the value 2 SD above the mean value of the zero standard) was 0.03 mU/L (0.0115 μg/L). The intraassay CV varied from 1.6 to 8.4% in the assay range 0.26–47 mU/L, with corresponding interassay CV of

2.0–9.9%. Until 2005 serum IGF-I concentrations were determined by RIA (Incstar, Stillwater, MN) with a detection limit of 1.5 nmol/L and an interassay CV below 11%. IGF-I is expressed as SD scores for age- and gender-related normal levels determined in the same laboratory (18). From 2005 onward, serum IGF-I concentration (nanograms per milliliter) was measured with an immunometric technique on the Immulite 2500 system (Diagnostic Products Corp., Los Angeles, CA). The intraassay CV was 5.0 and 7.5% at mean serum concentrations of 8 and 75 nmol/L, respectively. The IGF-I concentration was expressed as SD score, using the λ-μ-σ smoothed reference curves based on measurements in 906 healthy individuals (19).

Statistical analysis

All results are shown as mean±SD. Descriptive statistics were calculated. Student's t-tests were used when appropriate. $P < 0.05$ was considered to be statistically significant. Duration of follow-up in person-years was calculated for all patients as time between surgery until July 1, 2010, if patients were followed-up in our center, until date of secondary treatment in case of a recurrence, until last visit if patients were lost to follow-up, or until date of death in case patients had died. Incidence rates were calculated using number of cases divided over person-years of follow-up. Analyses were performed by SPSS package (version 16.0.2, 2008; SPSS, Chicago, IL).

Results

Baseline characteristics

We included 91 consecutive patients, 49 male and 42 female patients cured by transsphenoidal adenomectomy for a GH producing pituitary adenoma (Table 1). The mean age at the time of surgery was 46.8 ± 12.3 yr (range 18–76 yr). The mean disease duration before surgery was 9.0 ± 8.0 yr. Twenty-eight patients had a microadenoma (31%), 55 had a noninvasive macroadenoma (60%), and eight had an invasive macroadenoma (9%). Mean GH preoperative concentrations and IGF-I SD scores decreased significantly after surgery ($P < 0.001$, Table 1). Mean GH concentrations were 0.8 ± 1.0 μg/L, and IGF-I SD scores were 0.8 ± 2.1 at the end of follow-up.

Immediate postoperative assessment of adrenal function

Seven to 10 days after surgery, assessment of adrenal function was performed by CRH test (49%), ITT (43%), or by basal cortisol level in a minority of patients (2%). Three patients (3%) were not retested postoperatively because they had been cortisol dependent preoperatively. Data were missing in 2%. Sufficient adrenal function was observed in 36 of 44 patients according to the results of the CRH test, 35 of 39 patients according to ITT, and one of two patients according to basal cortisol. Thus, early postoperative adrenal insufficiency was observed in 16 patients (18%) including the three patients with preoperative secondary insufficiency. Hydrocortisone replacement was prescribed to 11 patients.

Table 1. Baseline characteristics and follow-up characteristics of patients with acromegaly cured by transsphenoidal surgery

	Patients (n=91)
M/F	49/42
Age at TNS (yrs)	46.8 ± 12.3 (range: 18–76)
Disease duration (yrs)	9.0 ± 8.0
Tumorclass (n(%))	
Class 1 – Microadenoma	28 (31%)
Class 2 – Non-invasive macroadenoma	55 (60%)
Class 3 – Invasive macroadenoma	8 (9%)
Preoperative GH (µg/L)	23.1 ± 27.1
Postoperative GH (µg/L)	0.9 ± 0.8
Follow-up GH (µg/L)	0.8 ± 1.0
Preoperative IGF-I SD	7.4 ± 4.2
Postoperative IGF-I SD	0.9 ± 1.9
Follow-up IGF-I SD	0.8 ± 2.1
Follow-up	
Pituitary deficiencies	
TSH	8 (9%)
LH/FSH	11 (12%)
GH	8 (14%)*

F, female; M, male; TNS, transnasosphenoidal surgery

Data are shown as mean ± SD unless mentioned otherwise. Significant decrease following surgery (P <0.001) for both GH and IGF-I SD. No difference between postoperative and follow-up concentations (P=ns). *Assessed in 58 patients by ITT.

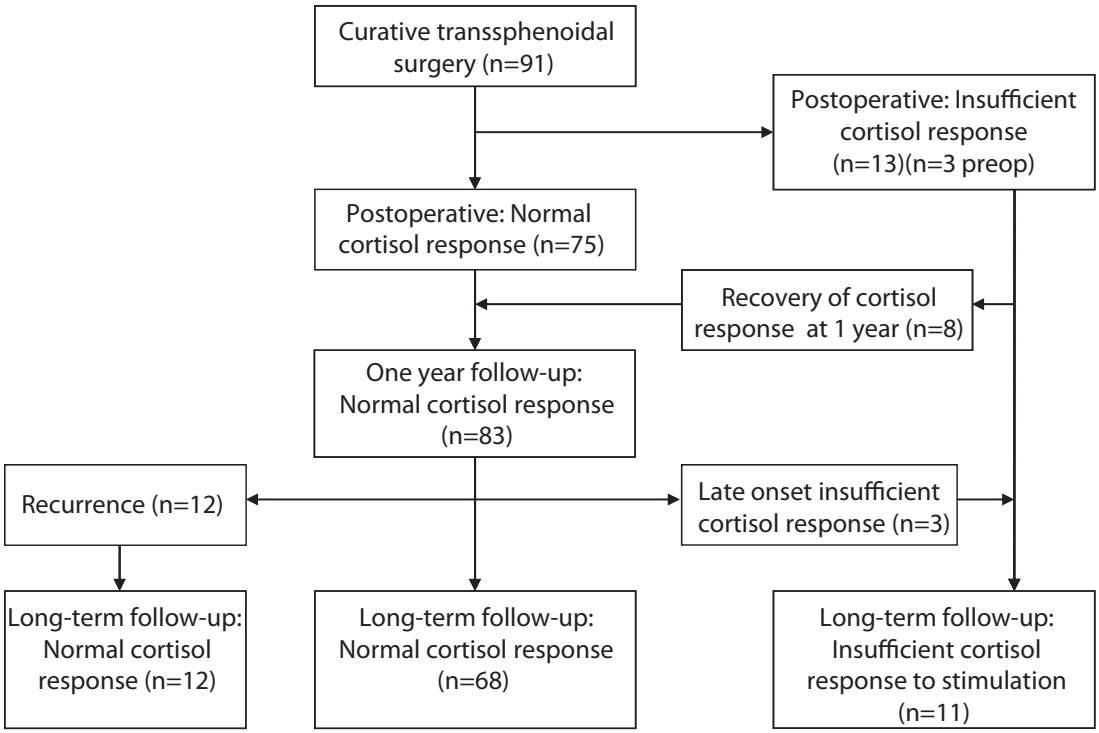

Figure 1. Flowchart of corticotrope function during long-term follow-up

Adrenal function 1 yr after surgery

At 1 yr postoperatively, the prevalence of adrenal insufficiency was 9% (eight of 91), three patients being diagnosed preoperatively and five patients diagnosed early postoperatively. These eight patients received hydrocortisone replacement therapy. Adrenal insufficiency was diagnosed by insufficient response to ITT (n=3), CRH (n=3), metyrapone test (n=1), or low basal cortisol of 20 nmol/L (n=1).

In the eight other patients with an early postoperative insufficient cortisol response to dynamic testing (CRH or ITT), retesting within the first year revealed normal adrenal function. The results of postoperative tests and follow-up tests in these patients are detailed in Table 2.

Adrenal function during prolonged follow-up

During prolonged follow-up, 262 ITT, 110 CRH tests, and 67 ACTH tests were performed in the patients cured by transsphenoidal surgery. Twelve patients with initial cure developed a recurrence of acromegaly (13%) a median of 8.7 yr (range 1.2–24.6 yr) after surgery. Consequently, 79 patients were in long-term cure after surgery only. Patients with

a recurrence of acromegaly were followed up until the date of the secondary treatment for the present analysis. At late evaluation (n=91), a median of 8.1 yr (1–31 yr) postoperatively, corticotrope function was assessed by ITT (67%), CRH (7%), ACTH (10%), or basal cortisol levels greater than 0.50 μmol/Liter (6%), whereas there were no data available in 10% of patients due to death (n=3) or loss to follow-up (n=6). During long-term follow-up of 1489 person-years, lateonset adrenal insufficiency developed in three patients (3%) 13, 18, and 24 yr postoperatively. The incidence rate for new-onset adrenal insufficiency was 2/1000 person-years. The clinical characteristics of these patients with late-onset adrenal insufficiency and their presenting symptoms of late adrenal deficiency are detailed in Table 3. All three patients had been treated for a noninvasive macroadenoma. Two patients had complaints of tiredness, dizziness, and/or general malaise. The third patient presented with unexplained hypoglycemias. Due to high age, no ITT was performed, but the ACTH test revealed insufficient response of cortisol. All patients improved clinically after replacement therapy. Thus, at the end of follow-up, adrenal insufficiency was present in 12% (11 of 91) of the patients in remission after transsphenoidal surgery. All these patients required hydrocortisone replacement therapy.

Table 2. Biochemical and clinical characteristics of patients with insufficient early postoperative adrenal function test, but recovery of adrenal function at repeat testing

Gender	Age at TSS (yr)	Postoperative test	Basal cortisol (µmol/L)	Peak cortisol (µmol/L)	Postoperative follow-up*	Follow-up test	Basal cortisol (µmol/L)	Peak cortisol (µmol/L)
M	38	CRH	0.26	0.34	Temporary hydrocortisone replacement	CRH	0.27	0.56
F	47	ITT	0.16	0.42	No Hydrocortisone replacement. Test and basal cortisol considered adequate.	basal cortisol	0.82	
M	46	ITT	0.13	0.47	No Hydrocortisone replacement	ITT	0.36	0.64
M	23	CRH	0.32	0.48	No Hydrocortisone replacement	ITT	0.28	0.78
M	23	CRH	0.34	0.48	No Hydrocortisone replacement	ITT	0.17	0.58
F	39	ITT	0.30	0.50	Temporary hydrocortisone replacement	ITT	0.15	0.57
M	52	CRH	0.37	0.52	Temporary hydrocortisone replacement	ITT	0.25	0.71
M	42	CRH	0.43	0.53	Hydrocortisone if needed.	ACTH	0.42	0.62

ACTH, adrenocorticotrope hormone; CRH, corticotrope releasing hormone; F, female; HC, hydrocortisone; ITT, insulin tolerance test; M, male; TSS, transsphenoidal surgery

*Postoperative management was decided by own physician.

Table 3. Characteristics of patients cured for acromegaly with late onset adrenocortical insufficiency

Gender	Age at TSS (yr)	Tumorclass*	Postoperative test	Basal Cortisol (µmol/L)	Peak cortisol (µmol/L)	Clinical follow-up	Test diagnose		Start HC after (yr)	Other pituitary deficiencies
							Stimulation test	*Results*		
M	33	2	ITT	0.09	0.55	Tiredness, malaise, chest pain, paresthesias	Metyrapone	11-DOC 44.3 cort 0.13	24	None
F	43	2	ITT	0.42	0.62	Headache, tiredness, astenia Yearly follow-up: basal cortisol 0.02 nmol/L	#		13	GH-TSH
F	67	2	ITT	0.34	0.60	DM II Unexplained hypoglycemia	ACTH –test**	Basal cort 0.16 Peak cort 0.47	18	GH-LH/FSH

ACTH, adrenocorticotrope hormone; cort, cortisol (µmol/L); CRH, corticotrope releasing hormone; DM, diabetes mellitus; 11-DOC, 11-deoxycortisol (nmol/L); F, female; FSH, follicle stimulating hormone; GH, growth hormone; HC, hydrocortisone; ITT, insulin tolerance test; LH, luteinizing hormone; M, male; TSS, transsphenoidal surgery; TSH, thyroid stimulating hormone

* Tumorclass 2 – non-invasive macroadenoma

#Based on low basal serum cortisol no stimulation test was performed.

** Due to high age at, no ITT was performed to confirm adrenal insufficiency

Discussion

The present study documents that new-onset adrenal insufficiency after successful surgical treatment for acromegaly in follow-up is not frequently observed. The prevalence of adrenal insufficiency was 9% 1 yr after surgery. In our well-characterized cohort of consecutive patients in remission after transsphenoidal surgery, the incidence rate of new-onset late adrenal insufficiency was only 2/1000 person-years during a long-term clinical follow-up. In accordance with the study by Ronchi *et al.* (3), our study demonstrates that HPA axis function may worsen over time, but adrenal insufficiency is an infrequent complication in patients in remission of acromegaly after surgery.

The discrepancies in the prevalence of adrenal insufficiency between the current study and the study by Ronchi *et al.* (3) may be explained by differences in study design and study population. In the study by Ronchi *et al.*, 16 of 36 patients had neuroradiological evidence of residual postoperative tumor remnants, and 16 were treated by somatostatin analogs. In addition, the authors used the low-dose ACTH stimulation test, which may lead to a false-negative response in 10% of healthy subjects (20).

Furthermore, Ronchi *et al.* used a cut-off value for cortisol of 500 nmol/L for the evaluation of the HPA axis, whereas we used mainly the ITT and CRH test with a cut-off value of 550 nmol/L. The ITT is generally regarded as the gold standard (7;21). Alternatively, the differences between the two studies may also be caused by patient selection and differences in surgical techniques. Ronchi *et al.* (3) observed a remarkably high prevalence of adrenal insufficiency in 32% of the patients treated by surgery and/or somatostatin analogs for acromegaly. However, only 16% of their patients required substitution therapy with hydrocortisone, in agreement with our data.

Potential caveats in our study include changed cortisol binding globulin (CBG) levels in acromegaly and the presence of postoperative GH deficiency. However, studies on the effect of GH on serum CBG

concentration are controversial. Some authors reported that GH administration in hypopituitary patients decrease CBG levels by approximately 20% (22–24), but other studies in larger cohorts did not observe a difference in CBG levels during GH treatment (25;26). Data on CBG concentrations in patients with active acromegaly are also scarce. One study investigated the effect of pegvisomant treatment on cortisol metabolism (27). These authors did not observe any change in serum CBG concentrations, although the majority of the patients reached normal IGF-I levels. Collectively these data indicate that the effect of GH on serum CBG levels is not unequivocal, especially in GH-deficient patients, and an increase in CBG concentrations after GH normalization in acromegaly has not been demonstrated.

GH has a strong impact on cortisol metabolism by its action on 11β-hydroxysteroid dehydrogenase, leading to increased cortisol-cortisone interconversion (28). For instance, GH replacement therapy in GH-deficient patients may unmask cortisol deficiency (23;26). In our study, untreated GH deficiency in the presence of a normal corticotrope function was present in only three of 58 patients (5%) with available GH measurements during ITT (data not shown), suggesting that it is unlikely that this significantly affected our results. Patients underwent surgery on a low-dose dexamethasone scheme, which may have influenced the test results, leading to overestimation of adrenal insufficiency shortly after surgery. Indeed, in eight patients with suboptimal cortisol response to ITT or CRH postoperatively, adrenal function normalized within 1 yr. This observation is in accordance with a recent study that compared the ITT response at 3 and 12 months postoperatively (29). In that study, cortisol peak responses increased by 17% and adrenal function had recovered in four of 20 patients with an insufficient cortisol peak response directly after surgery.

Recovery of preoperative adrenal insufficiency after transsphenoidal surgery has been described previously (30;31). Therefore, early postoperative testing may not reflect the definitive outcome of adrenal function. The outcome of these tests can be influenced by incipient GH or thyroid hormone deficiency, as discussed above (32). This observation emphasizes the importance of repeated dynamic tests also in patients with early postoperative insufficient response to adrenal function tests. After 1 yr, less frequent control of dynamic pituitary function may suffice in those patients with a confirmed normal adrenal function.

A recent meta analysis of 12 studies on the diagnostic value of basal cortisol values using summary receiver-operating characteristic curves showed an area under the curve of 0.79 (95% confidence interval 0.75–0.82). A lower cut-off value for basal cortisol less than 140 nmol/L (likelihood ratio > 9) was used to diagnose hypoadrenalism and an upper cut-off value of greater than 370 nmol/L (likelihood ratio < 0.15) was used to exclude hypoadrenalism. To be eligible for inclusion in this study, adult and pediatric subjects had to be suspected of adrenal insufficiency from pituitary disease longer than four wk from prolonged exogenous glucocorticoid administration. Only studies with ITT or metyrapone test as a reference test were included (33). It seems reasonable to use the guidelines as proposed by these authors. Thus, in patients with a basal serum cortisol greater than 370 nmol/L without complaints, the likelihood to have adrenal insufficiency is very low, and screening using basal cortisol may suffice in asymptomatic patients.

We had the opportunity to review long-term follow-up data in a carefully followed cohort and to have the availability of multiple tests in the vast majority of patients in the presence of few missing data. Nonetheless, limitations of our study are the retrospective nature of the study and the fact that patients had been tested using different cortisol stimulation tests and assays. However, this does not affect our conclusions because the ITT, CRH, and metyrapone tests are all accepted tests for the evaluation of HPA function, and we have used unchanged cut-off values of cortisol throughout the years. Nevertheless, several reports suggest that the sensitivity of the CRH test is less than that of the ITT (34–38). This conclusion is partly related to the cut-off value of CRH-stimulated cortisol responses. Unfortunately, there are no large studies of the CRH test in healthy subjects across ages, body mass index, and gender.

Therefore, we used a restrictive approach and retested subjects with an insufficient response to CRH by ITT. The CRH test may not detect hypothalamic insufficiency, whereas the ITT is a test for the hypothalamus-corticotrope- adrenal cortex ensemble. However, we have no a priori reason to assume hypothalamic damage in our patients because they had no previous pituitary irradiation or very large tumors impinging on the hypothalamus. Furthermore, our findings are strengthened by the consecutive nature of the patient series and the yearly assessment of the pituitary function. For the evaluation we used

preferably results of ITT. However, ongoing follow-up after the last ITT did not raise the suspicion of new adrenal deficiencies.

The recurrence of GH overproduction after initial cure by surgery may be due to either regrowth of residual tumor tissue or true recurrence (38–42). In our series we retested all patients cured by surgery at regular intervals. In our experience, recurrence of GH excess may occur, even after many years of postoperative cure documented by repeatedly normal IGF-I levels and normal GH nadir responses during the glucose tolerance test. This was also true after 1993, when a more sensitive GH assay was introduced. Even though this sequence of events may not exclude recurrence from persistent, but apparently longtime subclinical, postoperative adenomatous tissue, this observation indicates that the recurrence rate in our series is not merely the consequence of persistent postoperative disease. Moreover, in patients retested after surgical cure with regular intervals, we have previously documented that biochemical recurrence of GH excess after initial surgical cure clearly precedes radiological recurrence (42). Therefore, even in cases with biochemical recurrence of GH excess, it is highly unlikely that mass effects of adenomatous tissue were present. Finally, in the present study, we included the patients until the start of additional treatment of GH excess in the case of recurrent disease. Therefore, it is unlikely that recurrences of GH excess after years of biochemical remission affect our conclusions.

In conclusion, the incidence rate of late-onset adrenocortical insufficiency after successful surgery for acromegaly is very low (2/1000 person-years). We propose to repeat the dynamic test of HPA function 1 yr after surgery in patients with postoperative HPA insufficiency. Further research is required to assess whether yearly basal cortisol values may suffice to monitor adrenal function in asymptomatic patients. However, in case of low basal cortisol levels or symptoms suggestive of corticotrope insufficiency, additional dynamic testing should be performed.

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