Hypopituitarism : clinical assessment in different conditions

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Chapter 4

The use of an early postoperative CRH test to assess adrenal function after transsphenoidal surgery for pituitary adenomas

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Pituitary . 2011 Sep 9. [Epub ahead of print]

Abstract

Purpose: Transsphenoidal surgery (TS) is the treatment of choice for many pituitary tumors. Because TS may cause pituitary insufficiency in some of these patients, early postoperative assessment of pituitary function is essential for appropriate endocrine management. The aim of our study was to evaluate the clinical relevance of the CRH stimulation test in assessing postoperative pituitary-adrenal function.

Methods: We performed a retrospective analysis of 144 patients treated by TS between January 1990 and November 2009, in whom a CRH test and a second stimulation test was performed to assess adrenal function during follow-up. Patients with Cushing's disease were excluded. Hydrocortisone substitution was started if peak cortisol levels were < 550nmol/L.

Results: The cortisol response was insufficient in 42 (29%) and sufficient in 102 patients at the postoperative CRH test. Thirteen of 42 (30%) demonstrated a normal cortisol response during a second cortisol stimulation test. In 75 of the 102 patients with a sufficient response to CRH repeat testing revealed an insufficient cortisol response in 14 patients (14%). All but one had concomitant pituitary hormone deficits. There were no cases of adrenal crises during follow-up. Additional pituitary insufficiency was significantly more present ($P < 0.001$) in the group of patients with an abnormal response to CRH directly after surgery.

Conclusion: In this study a substitution strategy of hydrocortisone guided by the postoperative cortisol response to CRH appeared safe and did not result in any case of adrenal crises. However, the early postoperative CRH test does not reliably predict adrenal function after TS for pituitary adenomas in all patients, and retesting should be strongly considered.

Introduction

Transsphenoidal surgery (TS) is the treatment of choice for many pituitary tumors. TS may result in (additional) pituitary insufficiency in some of these patients (1–3). Therefore, accurate assessment of pituitary function is essential for appropriate management of postoperative patients after TS. In this respect, evaluation of the pituitary-adrenal axis is clinically relevant to assess the need for hydrocortisone replacement therapy at discharge.

The insulin tolerance test (ITT) is considered to be the gold standard for the evaluation of secondary adrenal insufficiency (4;5). Because there are contraindications for ITT in some patients, the CRH test, the metyrapone test or the ACTH stimulation test can be used as alternative dynamic tests to assess adrenal function (6–8). However, there is no international consensus for postoperative testing after pituitary surgery. We performed a structured literature search for articles that 1) evaluated the postoperative strategy for evaluation of adrenal function and 2) use of the CRH test to evaluate the pituitary-adrenal axis in postoperative patients after TS for pituitary adenomas, excluding manuscripts on patients with Cushing's disease. However, specific data on this topic are hardly available. Moreover, studies that compared CRH test and other dynamic test in other situations (*i.e.* in patients with (suspected) hypothalamic-pituitary insufficiency not specifically related to surgery) reported contradictory results (8;9). Therefore, at our center we developed a strategy for evaluation of patients after pituitary surgery in 1990 using the CRH test as the first postoperative test.

The aim of the present study was to assess the clinical relevance of the CRH stimulation test, as a part of this evaluation strategy, in assessing pituitary-adrenal function after TS. We performed a retrospective analysis of all patients treated by TS between January 1990 and November 2009, in whom a CRH test and a second stimulation test was performed to assess adrenal function during follow-up in non-Cushing patients.

Patients and methods

Study design

We performed a retrospective chart review of all patients, who had been treated by TS in the Leiden University Medical Center between January 1990 (when human CRH (hCRH) became available for routine clinical use) and November 2009. Patients with available data on a postsurgical CRH test, who also had a second (confirmation) test of adrenal function during follow-up were included. We excluded patients on high dose glucocorticoids, reoperation, postoperative cranial radiotherapy, and patients treated by TS for Cushing's disease.

The Medical Ethics Committee of our hospital declared that no formal ethical approval and written informed consent was needed for this anonymous retrospective chart review.

Endocrine assessment

According to the postoperative protocol, which has been implemented in our hospital, the pituitary-adrenal axis is assessed by CRH test, 7–10 days after surgery. The CRH test is performed after an overnight fast, after withdrawal of hydrocortisone for 24 hours, using 100 μg CRH (Corticoliberine, Ferring Farmaceuticals Hoofddorp, the Netherlands). Venous blood samples for measurement of ACTH and cortisol concentrations are collected at -15, 0, 15, 30, 45 and 60 minutes after infusion. A peak plasma cortisol of ≥ 550 nmol/L is considered to reflect a normal response (10;11).

In case of insufficient cortisol responses to CRH, hydrocortisone is prescribed (20 mg/day, divided in 3 doses). During follow-up, the treating endocrinologist decided on re-testing of the adrenal function. For the assessment of the HPA axis during follow-up either basal serum cortisol levels or a stimulation test was used. The ITT was performed after an overnight fast by intravenous administration of insulin (0.10 U/kg, Actrapid, Novo Nordisk Farma, Bagsvaerd, Denmark) to induce adequate hypoglycemia, defined as nadir glucose levels

< 2.2 mmol/L. Blood was collected for measurement of cortisol, ACTH and GH at -15, 0, 15, 30, 45, 60, 90 and 120 minutes after i.v. administration of insulin. Peak values of GH > 9 mU/L (corresponding with 3 µg/L) and cortisol of ≥ 550 nmol/L were considered to reflect normal pituitary function of GH and ACTH secretion (4;12–15).

For the ACTH test 1 µg Synacthen (Novartis Pharma, Arnhem, The Netherlands) was administered i.v. and cortisol levels were measured at -15, 0 and 30 minutes after infusion. A peak cortisol value of ≥ 550 nmol/L was considered to reflect normal adrenal reserve (16–18). In addition, a basal serum cortisol concentration of > 550 nmol/L was considered to reflect normal adrenal function (9).

In some patients a metyrapone test was used as a second test to assess pituitary adrenal function. Metyrapone (30 mg/kg, Metopiron, Novartis Pharma B.V., Arnhem, the Netherlands) was administered orally 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 (6;19;20).

Assays

Between 1986 and 1994, a fluorescence energy-transfer immunoassay Syva-Advance (Syva Company, Palo Alto, CA) was used, with an interassay variation coefficient of 3.6 – 6.1% and a detection limit of 50 nmol/L. From 1994, cortisol was measured by fluorescencepolarization assay on a TDx (Abbott Laboratories, Abbott Park, IL). The interassay variation coefficient is 5–6% above 500 nmol/L and amounts to 12% under 200 nmol/L. The detection limit is 20 nmol/L. The methods correlated well with each other, and therfore no correction factors were introduced for follow-up of patients. ACTH was determined by immunolimunimetric assay using an Immulite 2500 (Siemens Healthcare Diagnostics, Deerfield, IL, USA). The maximal inter-assay coefficient of variation (CV) was between 5.0 and 10.0%. During the insulin tolerance test glucose levels were measured using a Modular P800 (Roche Diagnostics, Mannheim, Germany).

For the measurement of 11-deoxycortisol a radioimmunoassay (RIA) of Diasource (previously Biosource Europe, Nivelles, Belgium) was used. CV was approximately 11%.

Free T_4, TSH, LH, FSH and prolactine blood levels were measured by electrochemoluminescent immunoassay (ECLIA), using a Modular E170, (Roche Diagnostics, Mannheim, Germany). The maximal inter-assay CV for these hormones was 5.0%. ACTH, GH and IGF-I were determined by immunolimunimetric assay using an Immulite 2500 (Siemens Healthcare Diagnostics, Deerfield, IL, USA). The maximal inter-assay CV was between 5.0 and 10.0%. Glucose levels were measured using a Modular P800 (Roche Diagnostics Mannheim, Germany) (CV is 3%). For measurement of estradiol levels a RIA (Orion Diagnostica, Espoo, Finland) was used (CV is 6% at 70 pmol/L). The estradiol detection limit was 20 pmol/L. Testosterone was measured using a RIA (Siemens Healthcare Diagnostics, Deerfield IL, USA). (CV is 20% at 1.0 nmol/L and 12% at 14 nmol/L). The detection limit was 0.2 nmol/L.

Statistical analysis

PAWS for Windows version 17.0 (SPSS Inc. Chicago, IL) was used to perform data analysis. Data were presented as mean ± SD unless otherwise mentioned. To evaluate the difference between peak cortisol of the direct postsurgical CRH test and the confirmation test during follow-up we used a paired t-test. A χ^2-test was used to evaluate the difference in prevalence of additional pituitary insufficiency in patients diagnosed with or without adrenal insufficiency based on the CRH stimulation test. The level of significance was set at $P \leq 0.05$.

Results

Patients

Between January 1990 and November 2009, 291 patients were treated by TS for non-functioning pituitary adenomas; NFA (n=160), GH-producing adenomas (n=96), prolactinomas (n=16) or other pituitary tumors (n=19) (Figure 1). A CRH test directly following surgery was not performed in 82 patients for several reasons (pituitary insufficiency prior to surgery n=29, follow-up in outpatient clinic n=11, use of corticosteroids surrounding surgery n=5, other stimulation test directly after surgery n=7, other n=30). Consequently, a CRH test was performed in 209 postoperative patients after TS. In 65 of these 209 patients, there was no additional adrenal test performed in follow-up between TS and referral for postoperative radiotherapy (n=24), repeat surgery (n=5), or death of the patient (n=10), or due to follow-up in another hospital (n=17) and lost to follow-up (n=9). Therefore, 144 patients were finally included in this study. Baseline characteristics of these 144 patients are presented in Table 1.

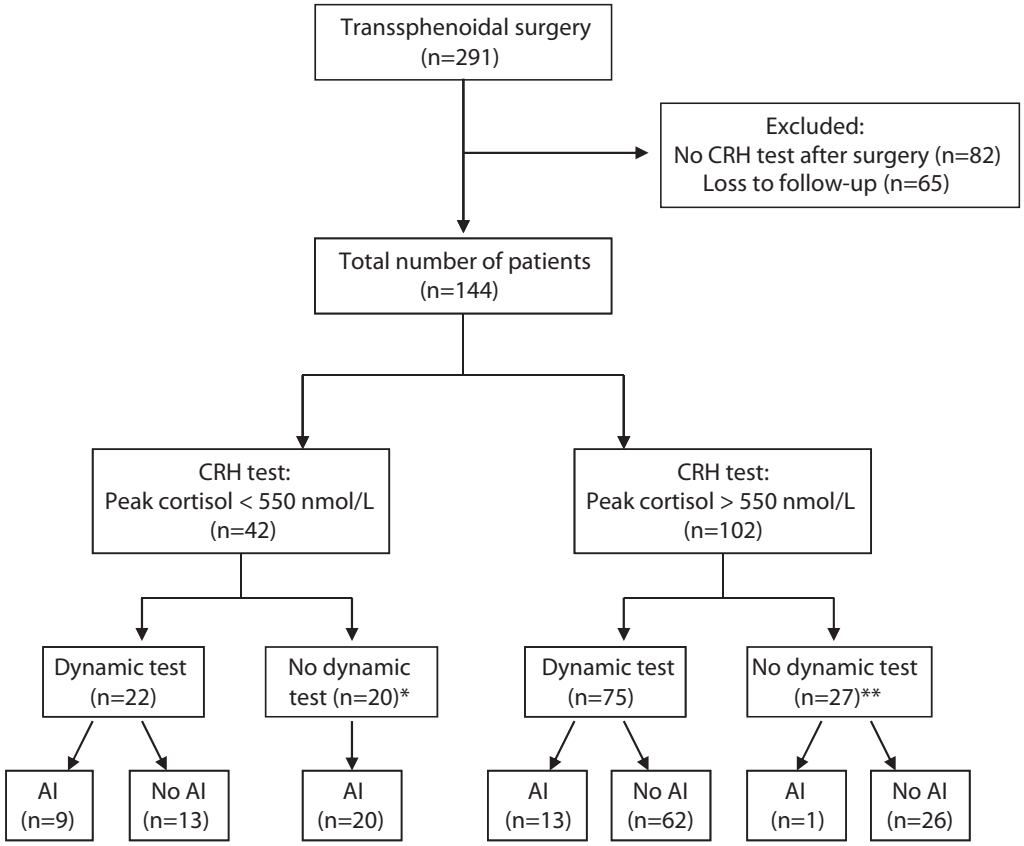

Figure 1. Flow-chart of patient selection and follow-up. *AI* = adrenal insufficiency.
*pre-existent panhypopituitarism before or immediately after surgery (n=12), pre-existent isolated severe adrenal insufficiency before surgery (n=4) or very low basal serum cortisol concentrations (mean 10 nmol/L) during follow-up after surgery (n=4).
**basal serum cortisol levels > 550 nmol/L (n=12), normal urine cortisol levels (n=3), short follow-up between repeated surgery or additional radiotherapy (n=2), and follow-up < 1 year (n=2) or unspecified reasons (n=7), basal serum cortisol < 110 nmol/L (n=1)

Table 1. Baseline characteristics total population

Baseline characteristics	**Number of patients (n=144)**
Gender (M/F)	71/73
Age (years)	50 (15–83)
Diagnosis (n):	
NFA	70
Acromegaly	63
Prolactinoma	6
Other pituitary tumors	5
Time between CRH test and confirmation test (months)	25.5 (2days*–219 months)
Confirmation test (n=97):	
ITT	55
CRH	16
ACTH stimulation test	21
Metyrapone test	5

* Basal serum cortisol was low, however CRH test peak cortisol 0.61; 2 days after CRH test a metyrapone test was performed

Patients with a decreased postoperative cortisol response to CRH (n=42)

The peak levels of cortisol during the postoperative CRH test classified 42 of the 144 patients with pituitary-adrenal insufficiency (peak cortisol < 550 nmol/L) (Figure 1). In 22 of these 42 patients with a median peak cortisol response to CRH of 480 (30–547) nmol/L, a second stimulation test was performed during follow-up: ITT (n=8), ACTH stimulation test (n=8), CRH stimulation test (n=5) and metyrapone test (n=1). These confirmation tests were performed with a median interval of 27.5 (1–139) months after the initial postoperative CRH test. Based on this repeat test, 9 of these 22 (41%) patients had persistent adrenal insufficiency [median initial cortisol response 356 (30–547) nmol/L; median cortisol response confirmation test 219 (3–514) nmol/L}, who received hydrocortisone (HC) replacement and 13 (59%) with a normal response, in whom HC was discontinued. In these 13 patients, the median peak cortisol level to postoperative CRH stimulation was 480 (340–543) nmol/L, whereas the median peak cortisol level during the second test were 672 (570–890) nmol/L ($P < 0.001$). The clinical characteristics of these patients are detailed in Table 2. Based on the results of the CRH test, four patients did not receive HC directly after surgery, or only if necessary. In two of these patients (Table 3; patient 2 and 8) the physician defined the HPA axis as normal based on the peak cortisol of the CRH test (540 and 543 nmol/L respectively). No clinical events were reported.

In 20 of these 42 patients with a median CRH-stimulated cortisol concentration of 194 (6–510) nmol/L, no additional stimulation test of adrenal function was performed during follow-up, but basal morning cortisol levels after the withdrawal of hydrocortisone for 18-24 h were used to assess the axis. Persistent adrenal insufficiency was considered to be present in these 20 patients because of pre-existent panhypopituitarism before or immediately after surgery (n=12), pre-existent isolated severe adrenal insufficiency before surgery (n=4) or very low basal serum cortisol concentrations (mean 10 nmol/L) during follow-up after surgery (n=4). Accordingly, all these patients received hydrocortisone supplementation directly after the post surgical CRH test until now.

Patients with a normal postoperative cortisol response to CRH (n=102)

The peak levels of cortisol during the postoperative CRH test classified 102 of the 144 patients with normal pituitary-adrenal function (peak cortisol > 550 nmol/L) (Figure 1). In 75 of these 102 patients, adrenal

function was assessed during follow-up using a second stimulation test and by basal postabsorptive cortisol levels only in the other 27 patients. These 27 patients were not subjected to a second stimulation test because of basal serum cortisol levels > 550 nmol/L (n=12), normal urine cortisol levels (n=3), short follow-up between repeated surgery or additional radiotherapy (n=2), and follow-up < 1 yr (n=2) or unspecified reasons (n=7). One patient returned within three months after surgery with complaints and basal postabsorptive serum cortisol levels of 90 nmol/L and HC was started without additional stimulation test. The ITT was used in 49 of the 75 patients, the CRH test in 11 patients, the ACTH stimulation test in 11, and the metyrapone test in four patients. A normal response to these tests was found in 62 patients. However, 13 patients had an insufficient adrenal response to these tests. With the inclusion of the patient with very low basal serum cortisol levels (see above), 14 patients were classified as adrenal insufficient (Table 3). Thirteen of these 14 patients had been diagnosed with any other additional pituitary insufficiencies and 8 of these patients (57%) had panhypopituitarism. Six patients already received HC directly after surgery. None of these 14 patients experienced any clinical event related to cortisol deficiency.

Prevalence of additional pituitary insufficiency

A total of 73 patients had additional pituitary insufficiency. The prevalence of additional pituitary insufficiency was significantly higher in patients diagnosed with an insufficient CRH stimulation test after surgery compared to patients with a normal test result (any hypopituitarism $P < 0.001$; GHD $P < 0.001$; TSH deficiency $P < 0.001$; LH/FSH deficiency $P = 0.001$).

Table 2. Patients incorrectly diagnosed with adrenal insufficiency based on the CRH test directly after surgery

	Gender	Age at time of surgery (yrs)	Diagnosis	CHR test Peak cortisol (nmol/L)	HC after Surgery (y/n)	Follow-up (years)	Confirmation test	Peak cortisol (nmol/L)	Other deficiencies	Follow-up	Clinical event (y/n)
1	M	53	NFA	410	y	3 mnths	ACTH	890	LH/FSH, GHD	No optimal reaction CRH test, HC discontinued before confirmation test. After 3 years ITT peak cortisol 860 nmol/L	n
2	M	48	Acromegaly	540	n	3.8	CRH	790	None	After CRH test HPA axis defined as normal, no HC	n
3	M	23	Acromegaly	480	n	4.9	ITT	780	None	After CRH test another CRH test and 24h urine still not sufficient.; ITT after 4 years insufficient	n
4	F	26	Prolactinoma	480	y	8.9	ITT	750	DI	HC until next outpatient appointment; 5 yrs loss to follow-up; recurrence of prolactinoma treatment with Dostinex. Did not use HC. 8 yrs after surgery 2 sufficient ACTH tests and 1 yr later normal ITT	n
5	M	53	NFA	440	y	1 mnth	CRH	710	GHD	HC discontinued after CRH test. (9 yrs after surgery RT)	n
6	F	62	NFA	469	y	7 mnths	ITT	696	GHD	After 4 months ACTH peak cortisol 580 therefore stop HC. 3 months later ITT	n

Table 2. Continued

	Gender	Age at time of surgery (yrs)	Diagnosis	CHR test Peak cortisol (nmol/L)	HC after Surgery (y/n)	Follow-up (years)	Confirmation test	Peak cortisol (nmol/L)	Other deficiencies	Follow-up	Clinical event (y/n)
7	M	59	NFA	457	y	7 mnths	ACTH	672	TSH, LH/FSH, GHD	HC discontinued; after 5 months ACTH test insufficient peak cortisol 445 nmol/L. Followed by 3 more ACTH tests (7–9months after surgery) all normal cortisol response. ITT 1 yr after surgery however nadir 2.3 mmol/L; cortisol peak 574 nmol/L.	n
8	F	72	Acromegaly	543	n	1.2	CRH	665	None	HPA axis defined as normal, no HC	n
9	F	56	NFA	520	y	3.9	ITT	657	Panhypopit	After 6 months ACTH test normal; 1 month later ITT peak cortisol 550 nmol; HC lowered to 10 mg/day. 10 months later ITT normal response cortisol; stop HC. 2 yrs later another ITT	n
10	M	38	Acromegaly	340	y	10.3	ITT	634	None	Received HC before surgery, discontinued after surgery followed by CRH test after 3 months; peak cortisol 560 nmol/L. 10 yrs after surgery ACTH test followed by ITT both normal cortisol responses.	n

	Gender	Age at time of surgery (yrs)	Diagnosis	CHR test Peak cortisol (nmol/L)	HC after Surgery (y/n)	Follow-up (years)	Confirmation test	Peak cortisol (nmol/L)	Other deficiencies	Follow-up	Clinical event (y/n)
11	M	42	Acromegaly	530	i.n.	11.6	ACTH	618	None	Based on CRH only HC if necessary. Shortly after CRH test ACTH test with normal cortisol response; no HC necessary. 11 yrs later another ACTH test	n
12	F	42	NFA	482	y	1.3	CRH	606	None	6 months after surgery 1st ACTH test; insufficient cortisol response; followed by 4 ACTH tests within 6 months. All insufficient cortisol response. Followed by a CRH tests with a sufficient response.	n
13	F	39	Acromegaly	500	y	4.1	ITT	570	None	4 months after surgery 2nd CRH test still insufficient cortisol response; continue HC. 1 yr later ITT; peak cortisol 520 nmol/L. 3 yrs later 2nd ITT sufficient stop HC	n

M, male; F, female; NFA, non functioning adenoma; n, no; y, yes; i.n., if necessary; DI, diabetes insipidus; ITT, insulin tolerance test; CRH, corticotropin releasing hormone; HC, hydrocortisone; GHD, growth hormone deficiency.

Table 3. Patients who appeared to be adrenal insufficient based on a second test or basal serum cortisol concentration during follow-up

	Gender	Age at time of surgery (yrs)	Diagnosis	CHR test Peak cortisol (nmol/L)	HC after Surgery (y/n)	Follow-up (years)	Confirmation test	Peak cortisol (nmol/L)	Other deficiencies	Follow-up	Clinical event (y/n)
1	M	55	NFA	750	n	2 months	ITT	512	Panhypopit	Before surgery panhypopituitarism; ITT after 2 months insufficiënt	n
2	M	50	NFA	690	n	1.7	ITT	510	Panhypopit	Not all results known when patient left hospital. Appeared to be TSH- and GH deficient. Outpatient follow-up 1st ITT sufficient; 2nd ITT insufficient	n
3	M	19	NFA	780	n	6.5	ITT	480	Panhypopit	After surgery gonadotrophic deficiency; ITT 2002 sufficient; ITT insufficiënt; corticotrope and GH deficiency; start suppletion	n
4	F	50	NFA	640	y	1.8	ITT	410	Panhypopit	After surgery HC ; follow-up after 1 year Metyrapone test insufficient; 1 yr later ITT still insufficient	n
5	F	53	NFA	1100	y	2 months	Metyrapone test	90	TSH, GHD	Before surgery TSH deficiency and hypocortisolism; Start HC after surgery; 2 mnths after surgery ACTH and Metyrapone test both insufficient	n
6	M	60	NFA	600	y	6 months	ITT	200	Panhypopit	Received HC before surgery; continued after surgery; follow-up after 6 months	n

	Gender	Age at time of surgery (yrs)	Diagnosis	CHR test Peak cortisol (nmol/L)	HC after Surgery (y/n)	Follow-up (years)	Confirmation test	Peak cortisol (nmol/L)	Other deficiencies	Follow-up	Clinical event (y/n)
7	F	57	NFA	670	n	3.4	Metyrapone test	190 159	Panhypopit	1 yr after surgery new CRH test sufficient. Complaints of tiredness. 2 yrs later Metyrapone insufficiënt.	n
8	M	54	NFA	670	n	4.3	ACTH 1 ug	170	Panhypopit	After surgery gonadotropic and GH deficiency. After 3 yrs start rhGH; 2 yrs later low cortisol 24h urine and hypothyroidism. Euthyreotic state ACTH test insufficiënt start HC	n
9	F	78	NFA	620	n	3 months	Metyrapone test	120 84.9	None	Cardial problems; follow-up in outpatient clinic	n
10	F	77	NFA	610	y	2 days	Metyrapone test	90 79.5	TSH, DI	Based on low basal serum cortisol levels start HC; 2 days after CRH metyrapone test insufficient.	n
11	F	50	NFA	770	n	7	Metyrapone test	90 107	Gonadotrope, GHD	Several years no complaints no insufficiency; 2002 ITT GHD followed by therapy; 2004 metyrapone insufficient	n

Table 3. Continued

	Gender	Age at time of surgery (yrs)	Diagnosis	CHR test Peak cortisol (nmol/L)	HC after Surgery (y/n)	Follow-up (years)	Confirmation test	Peak cortisol (nmol/L)	Other deficiencies	Follow-up	Clinical event (y/n)
12	F	67	NFA	600	y	1.4	ITT	4	Panhypopit	Directly post surgery probably panhypopit because of lesion/rupture pituitary stalk. No basal ACTH production with stimulation after CRH; Start HC	n
13	M	38	NFA	797	n	3 months	Basal serum cortisol	90	Panhypopit	Before surgery panhypopit; CRH test normal. 3 months after surgery complaints with low basal serum cortisol. Start HC	n
14	M	39	NFA	660	y	5 months	ACTH-test	300	GHD, gonadotrope, DI	Before surgery panhypopituitarism. Probably HC during CRH test after surgery.	n

M, male; F, female; NFA, non functioning adenoma; n, no; y, yes; DI, diabetes insipidus; ITT, insulin tolerance test; CRH, corticotropin releasing hormone; HC, hydrocortisone; GHD, growth hormone deficiency.

Discussion

This study evaluated the postoperative response of cortisol to CRH stimulation in a large cohort of patients after TS for pituitary adenomas compared with the adrenal function assessed during postoperative follow-up. The second adrenal function test documented a normal cortisol response in 31% of the patients with a decreased cortisol response to CRH stimulation directly after surgery. Conversely, the second adrenal stimulation test documented an insufficient cortisol response in 14% of the patients with a normal cortisol response to direct postoperative CRH stimulation. Therefore, the postoperative CRH test does not reliably predict adrenal function after TS for pituitary adenomas in all patients. Nonetheless, our substitution strategy of hydrocortisone guided by the postoperative cortisol responses to CRH did not result in any case of adrenal crises in our patients.

Although CRH stimulation has been incorporated in the diagnostic procedures of ACTH dependent Cushing's syndrome (21–23), reports on the use of CRH stimulation to assess cortisol dependency after transsphenoidal surgery for other pituitary adenomas are scarce. We found three publications that assessed pituitary function using CRH, but these were not specifically in patients after transsphenoidal surgery (8;9). Dullaart *et al.* (9) and Schmidt *et al.* (8) compared the CRH test with basal serum cortisol levels and found no higher diagnostic applicability of the CRH test to basal morning cortisol levels. In contrast, Maghnie *et al.* concluded that the CRH test provided better results than the short Synacthen test (SST) and low-dose short Synacthen test (LDSST), and that CRH may be useful in patients who have a contraindication for ITT (6).

In the current study, the postoperative CRH stimulation test classified 42 of the 144 patients with hypocortisolism. However, 13 of these patients had sufficient adrenal function during follow-up. There are several explanations for these discrepant results. They may be related to differences in cut-off values of the different tests. Regularly accepted

cut-off values (500-550 nmol/L) have been defined for the ITT, which still remains the gold standard test for the assessment of the HPA axis. For the CRH test, some authors have proposed different cut-off values for peak cortisol responses. For example, Schmidt *et al.*(8) reported an optimal peak cortisol cut-off of < 377 nmol/L, yielding a 96% specificity, but poor sensitivity of 76% for the diagnosis of adrenal insufficiency (8). A sensitivity of 100% was reached using a peak cortisol levels of 514 nmol/L (with a specificity of 32%), and 100% specificity with peak cortisol levels of 349 nmol/L (sensitivity 66%). Dullaart *et al.* found that a peak cortisol value of 420 nmol/L reflected 100% specificity, but 100% sensitivity for the CRH test was only reached using a peak cortisol of 615 nmol/L. Because in our center the CRH test is used as a screening test for hypocortisolism after TS to identify those patients that require hydrocortisone supplementation, we applied a generally accepted stringent criterion of 550 nmol/L. The data indicate that this choice for a higher sensitivity of the CRH test is at the expense of a lower specificity. In other words, using this strategy a higher proportion of patients will be incorrectly diagnosed with adrenal insufficiency. Based on the available literature the use of a cut-off levels of peak cortisol of 514 nmol/L would have resulted in 4/13 patients which would not have been diagnosed with adrenal insufficiency, but with the criteria suggested by Dullaart *et al.* even more patients would have had discrepant results (8;9).

Recovery of preoperative adrenal insufficiency following TS has been described previously (24;25). In a recent study that compared the ITT response at 3 and 12 months after TS, recovery of adrenal function was demonstrated within the first year (26). In agreement, we found a normal function of the HPA axis in eight patients within the first year after surgery who were initially diagnosed as being adrenal insufficient, indicating the necessity of an extensive follow-up in patients after surgery within one year.

In the current study, the postoperative CRH test classified 102 of the 144 patients as having a normal functioning of the HPA axis based on the post-operative CRH test. Fourteen percent of these patients later proved to have hypocortisolism by a second test. These discrepant test results can be potentially life-threatening because these patients are at risk for adrenal crises. It is possible that additional pituitary insufficiencies affected pituitary-adrenal function. Growth hormone and thyroid hormone deficiency can influence these test results. Growth hormone replacement

therapy in patients with GH deficiency may also play an important role because of the influence of GH on the cortisol metabolism. Growth hormone stimulates 11-β hydroxysteroid dehydrogenase (11βHSD-1), leading to increased cortisol-cortisone interconversion (27) . The use of GH replacement therapy in GH deficient patients may therefore unmask cortisol deficiency (28;29). This may also be the case in some of our patients, because their adrenal insufficiency became clear after start of rhGH therapy. Despite all the confounding factors none of our patients had a clinical event.

In conclusion, the CRH test can be safely used to guide hydrocortisone substitution after TS. Nonetheless, the cortisol response to this test cannot reliably predict adrenal function in all patients during longer follow-up after TS. We therefore recommend to perform a second test of pituitary adrenal function during longer follow-up, e.g. 3–6 months after surgery (see Figure 2). This approach is not required in patients with an impaired postoperative cortisol response to CRH, who have multiple pituitary insufficiencies.

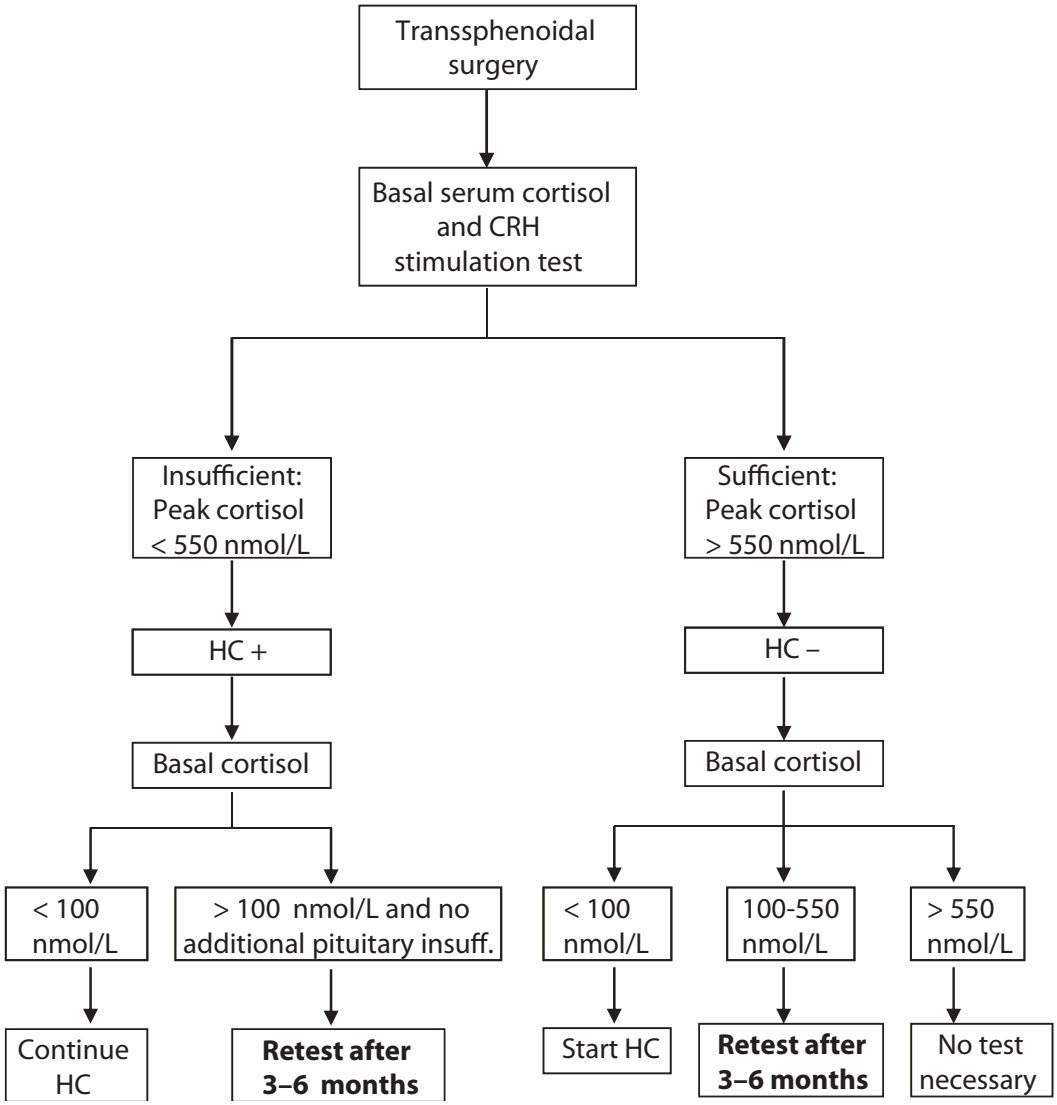

Figure 2. Proposed algorithm for the postoperative follow-up of adrenal function in non ACTH dependent pituitary disease (HC; hydrocortisone)

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