Clinical consequences of endogenous and exogenous glucocorticoid excess

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Chapter 8

Adrenal crisis in treated Cushing's disease and Cushing's syndrome patients

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Abstract

Background
Adrenal crisis, the most feared complication of adrenal insufficiency, is a potentially life-threatening state of acute glucocorticoid deficiency. After successful surgery for Cushing's syndrome, many patients develop (transient) adrenal insufficiency. The incidence of adrenal crisis in patients treated for hypercortisolism is unknown.

Methods
Cohort study including consecutive patients with Cushing's syndrome with adrenal insufficiency after surgery from Leiden and Berlin from 2000-2015. We summarized incidence of adrenal crisis, compared patients with and without adrenal crisis regarding potential risk factors for its occurrence, and assessed the effect of better education in time on incidence of adrenal crisis.

Results
We included 106 patients, of whom 19 patients had a total of 41 adrenal crises. There were 9.0 crises per 100 patient-years at risk (95% confidence interval [CI]: 6.7-12.0). All crises occurred while on hydrocortisone replacement. The risk ratio for a recurrent crisis was 2.3 (95% CI: 1.2-4.6). No clear change in incidence of adrenal crisis due to better education in time was observed. There was no difference in recurrence rate between patients with, and without any crisis, but patients with adrenal crisis had more often pituitary deficiencies.

Conclusions
The incidence of adrenal crises after treatment for Cushing's syndrome is substantial, and patients who suffered from an adrenal crisis have higher risk for recurrent crisis. However, further risk factor analysis is needed to identify risks for a first crisis. Effective education methods to prevent adrenal crises should be identified and implemented, including stress instructions by trained nursing staff before hospital discharge.

Introduction

An adrenal crisis is a potentially life-threatening situation of an acute state of glucocorticoid deficiency, which can develop after any situation of increased demand for stress hormones, such as intercurrent illness or psychological stress, and is the most feared complication of adrenal insufficiency (1). The incidence of adrenal crisis in the heterogeneous population of patients with adrenal insufficiency is estimated to be 4.1 to 9.3 per 100 patient-years (2-9). There is no consensus on the definition of (imminent) adrenal insufficiency. However, the proposed definition by Allolio *et al.* is useful for clinical practice: a combination of 1) Major impairment of general health with at least two of the following signs/symptoms: hypotension, nausea or vomiting, severe fatigue, fever, somnolence, hyponatremia or hyperkalemia, hypoglycemia, and 2) Parenteral glucocorticoid administration followed by clinical improvement (10). A recent Dutch guideline developed by a multi-disciplinary group, that also included patient representatives, provides clear guidance on when to act to prevent adrenal crisis in daily life, e.g. in case of elective surgical procedures or acute illness with intensive care admission, and how to treat acute adrenal crisis (11).

Cushing's syndrome is the result of a prolonged state of endogenous hypercortisolism. This can be adrenocorticotropic hormone (ACTH)-dependent (e.g. Cushing's disease) or ACTH-independent (e.g. an adrenal cortisol-producing adenoma) (12). Excess of glucocorticoids causes osteoporosis, central obesity, insulin resistance, dyslipidemia, hypertension, hypercoagulability, cognitive dysfunction, and neuropsychiatric disorders (13, 14). First-choice treatment is transsphenoidal selective adenomectomy for Cushing's disease (15), surgical removal of the tumor in case of ectopic ACTH-producing tumors, and adrenalectomy for an adrenal adenoma (16).

After successful surgery, patients with Cushing's disease develop (transient) severe adrenal insufficiency due to suppression of the physiological hypothalamic-pituitary-adrenal (HPA) axis by the pathological secretion of ACTH by the adenoma, for which hydrocortisone replacement therapy is needed. A significant number of these patients even need life-long replacement therapy, because of incomplete recovery of the HPA-axis either due to isolated downregulation of the adrenal glands or because of pituitary function loss, which is seen in 42% of patients after 5 years of follow-up (17). The incidence of adrenal crisis in the subset of patients with a history of hypercortisolism is unknown. Due to long-standing hypercortisolism, the activity of the HPA-axis may have altered the response to cortisol deficiency in patients treated for Cushing's syndrome (including Cushing's disease) compared to other adrenal insufficient patients. The history of hypercortisolism and potential occurrence of corticosteroid withdrawal syndrome and a phase of lowering replacement doses may complicate diagnosis and awareness in these patients, as both patients and doctors

may not recognize early symptoms of adrenal crisis in time. Corticosteroid withdrawal syndrome can occur in patients with previous hypercortisolism despite apparently acceptable cortisol concentrations, meaning that these patients need higher replacement doses of hydrocortisone than other adrenal insufficient patients. This may suggest that they are at higher risk of an adrenal crisis if they receive normal replacement doses that result in apparently acceptable cortisol concentrations (18).

For clinical practice, it is important to know how often adrenal crisis occurs and what the possible risk factors are in the population of patients in the aftermath of an episode of endogenous hypercortisolism.

Study aims

The primary study aim was to summarize the incidence of adrenal crisis, defined as an acute impairment of general health requiring hospital admission (excluding emergency room visit only) and administration of intravenous glucocorticoids, with subsequent resolution of symptoms, in a population of patients with Cushing's syndrome treated by transsphenoidal pituitary surgery or adrenalectomy during the time that they were adrenal insufficient. Secondary study aims were to find risk factors identifying patients with Cushing's syndrome who may be at higher risk for an adrenal crisis after surgical treatment, to describe the course and underlying cause of adrenal crisis, and to assess a potential change in incidence of adrenal crises due to better education in recent time.

Methods

Study population

Consecutive patients with Cushing's disease and adrenal Cushing's syndrome from the Leiden University Medical Center and the Charité Universitätsmedizin Berlin were included in this cohort study. Patients with an adrenal carcinoma were excluded. Patients were included between January 1st 2000 and December 31st 2015. Only patients with adrenal insufficiency and glucocorticoid dependency after transsphenoidal pituitary surgery or adrenalectomy were included, as this constitutes the population at risk for an adrenal crisis. There were no restrictions in prior or adjuvant treatment, such as reoperation, prior or adjuvant radiotherapy or pre-operative cortisol-lowering medication.

The diagnostic process for ACTH-dependent Cushing's syndrome was described previously (19). For ACTH-independent Cushing's syndrome, the same criteria were used, except that ACTH had to be suppressed, and that adrenal imaging was

performed by either magnetic resonance imaging (MRI) or computed tomography (CT). Due to the use of different assays, cut-off levels for the used tests varied between both study centers and over time.

Transsphenoidal adenomectomy (TSA) was the first-choice treatment for Cushing's disease. One patient underwent bilateral adrenalectomy, because no pituitary adenoma was visualized on MRI and no lateralization was present during inferior petrosal sinus sampling, but also no ectopic ACTH-producing source was found. For patients with adrenal Cushing's syndrome, adrenalectomy was the first-choice treatment. Details of postoperative evaluation as well as definitions of remission, recurrence and persistent disease were presented previously (19). We included the time period that a patient was hydrocortisone dependent, as explained more extensively under "follow-up". During disease recurrence, patients were excluded from our study, but they could re-enter the study if after further treatment, they were again hydrocortisone dependent. Starting from three months postoperatively, potential normalization of the HPA-axis was tested dynamically with synthetic ACTH, corticotropin-releasing hormone (CRH), or insulin tolerance test (ITT). The HPA-axis was considered normalized if the dynamic test showed a normal test result, and consequently hydrocortisone replacement was discontinued.

Study outcomes and follow-up

Primary outcome of interest was adrenal crisis. Further outcomes of interest were mortality, (surgical) outcome including recurrent disease, and complications. Unless otherwise specified, outcomes were reported in relation to the first surgery.

Adrenal crisis was defined as an acute impairment of general health requiring hospital admission (not only emergency room, as emergency room adrenal crises could not be scored reliably) and administration of intravenous glucocorticoids, after which a resolution of symptoms followed (10). Self-treatment for adrenal crisis at home was not included as endpoint, as the accuracy of this diagnosis cannot be guaranteed. Regarding adrenal crisis, the total number of crises and the total number of patient-years at risk were summarized, as well as the number of crises per patient with at least one crisis, the type of hospital admission (regular ward or intensive care), duration of hospital stay in days, hydrocortisone dose before hospital admission for the adrenal crisis in mg/day (in case of a crisis before first hospital release after surgery, the last dose given before start of symptoms was entered), and, at hospital admission for the adrenal crisis, the number of patients with a subphysiological dose of hydrocortisone replacement (<20 mg/day), the number of patients with an infection, and the number of patients with psychological stress.

Besides recurrent disease, the following variables were described: hydrocortisone release dose from the hospital after the first surgery in mg/day, number of patients with restoration of the HPA-axis within one year after first surgery, and adjuvant treatment (radiotherapy, transsphenoidal adenomectomy, adrenalectomy, and medical treatment).

Complications (measured ≤3 months after first surgery) included diabetes insipidus (requiring medication at least once) and anterior pituitary deficiency other than ACTH requiring medication. Complications were described only for patients that underwent transsphenoidal adenomectomy.

We followed patients from date of surgery for Cushing's syndrome until death, loss to follow-up, or December 31st 2016, whichever came first. Patients were followed only during the period that they were at risk of having an adrenal crisis, i.e. from the moment they had adrenal insufficiency and glucocorticoid dependency until normalizing adrenal function, evidenced by clinical stop of hydrocortisone replacement and at least one normal dynamic test (ACTH, CRH or ITT). Patients were potentially included again after a period of normal adrenal function if they once more experienced adrenal insufficiency and glucocorticoid dependency after a repeat surgical procedure or radiotherapy.

Presurgical information was collected regarding diagnosis, comorbidities (hypertension, diabetes mellitus, dyslipidemia), and cortisol-lowering medical treatment prior to surgery. Pituitary tumor size was divided into microadenomas (≤10 mm) and macroadenomas (>10 mm).

All eligible patients were included in this study to prevent selection bias. However, selective loss to follow-up could have led to selection bias. Confounding was assessed as a potential source of bias by comparing baseline characteristics between groups.

Statistical analysis

In the contingency tables, patients with at least one adrenal crisis were compared to patients without any adrenal crisis: 1) Demographic characteristics and medical history (age at diagnosis, sex, duration of follow-up, Cushing's syndrome Severity Index (CSI) score (20), type of surgical treatment, comorbidities, tumor size for pituitary adenomas, and cortisol-lowering medical treatment prior to surgery), and 2) Adrenal crisis details, (surgical) outcome, and complications. The difference between the two study groups was tested with an unpaired T-test for continuous outcomes and with the two-sample test of proportions for outcomes reported as proportions. These tables were also stratified by study center. If data were missing for ≥5% of patients, this was marked in the tables.

The Andersen-Gill adaptation of the Cox proportional hazard model was used to analyze the effect of the following variables on occurrence of an adrenal crisis: study center (Leiden versus Berlin) and etiology of Cushing's syndrome (21). Univariate and multivariate analyses were performed. Only hydrocortisone-dependent time was included in the model, because this was the patient-time at risk for an adrenal crisis. By using the Andersen-Gill model, we were able to include recurrent adrenal crisis and take into account time between crises. Hydrocortisone replacement dose before hospital admission for adrenal crisis was related to the time between last surgery and the occurrence of adrenal crisis. This was the only analysis in which time since last surgery before adrenal crisis was used, as only patients with at least one crisis were included in this analysis and we were specifically interested in time since last surgery for this outcome. Prior adrenal crisis was related to risk of recurrent adrenal crisis by calculating the risk ratio, which was performed by dividing risk of recurrent crisis for patients with a first adrenal crisis by the risk of a first adrenal crisis for all included patients. Number of adrenal crises per 100 patient-years at risk was stratified by time period (2000-2004, 2005-2009, 2010-2016), to assess a change in incidence due to better education in time.

Statistical analyses were performed with IBM SPSS Statistics 23.0 (IBM Corp, Armonk, NY, USA), and with Stata 14.2 (Stata Corp., College Station, TX, USA) for the Andersen-Gill model and the two-sample test of proportions (command: prtesti) to calculate the difference between two proportions with 95% confidence interval (CI), as this was not provided by SPSS. Patients gave informed consent to use their data for scientific research. Permission was granted from the ethical committees in the LUMC and Charité Universitätsmedizin. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used for reporting (22).

Results

Study population

In total, 106 patients were included in this study (66 from Leiden and 40 from Berlin), of whom nineteen patients (17.9%) suffered from at least one adrenal crisis. There was no difference in sex or age between both groups. For the nineteen patients with adrenal crisis, mean age was 46.2 years (range: 16-72), and most (n=14, 73.7%) were female. Of the 87 patients without adrenal crisis, mean age was 42.9 years (range: 10-80), and 68 (78.2%) were female.

At diagnosis of Cushing's syndrome, patients with adrenal crises had more often diabetes mellitus (68.4% versus 24.1%), and more often macroadenomas (53.8% versus 24.6%) than patients without adrenal crises. There was no difference in Cushing's

syndrome Severity Index score between both groups. Twenty patients were lost to follow-up after an average of 81.2 months (range 3-165), of whom four with at least one crisis (21% out of 19 patients with at least one crisis) and sixteen without any crisis (18% out of 87 patients without any crisis). For a detailed description of demographic characteristics, see Table 1. Results per study center can be found in Supplemental Data 1.

In Leiden, patients received a lower hydrocortisone replacement dose at hospital discharge postoperatively than in Berlin (median of 20 mg/day [interquartile range (IQR): 20-40; mean 25 mg/day] versus 30 mg/day [IQR: 25-50; mean 35 mg/day]), in accordance with the institutional protocols. However, in Berlin, the hydrocortisone replacement dose at hospital discharge was higher in patients with an adrenal crisis (median 50 mg/day), which was not observed in patients from Leiden.

Table 1: Demographic characteristics.

	Adrenal crisis		**No adrenal crisis**		**Tested difference (95% CI)**
	N	**%**	**N**	**%**	
Total number of patients	19	100.0	87	100.0	
*Age at diagnosis, years**	46.2	12.5	42.9	14.8	3.3 (-4.0 to 10.5)
Sex (female)	14	73.7	68	78.2	4.5% (-17.1% to 26.1%)
*Duration of follow-up (years)^*	6.3	4.6-11.3	7.8	3.7-11.7	0.5 (-1.7 to 2.7)
*Cushing's syndrome Severity Index score**	6.7	2.5	6.7	2.4	0.1 (-1.2 to 1.3)
Surgical treatment: transsphenoidal pituitary surgery	14	73.7	64	73.6	0.1% (-21.8% to 22.0%)
Comorbidities at diagnosis					
Hypertension	13	68.4	66	75.9	7.5% (-15.3% to 30.3%)
Diabetes mellitus	13	68.4	21	24.1	44.3% (21.5% to 67.1%)
Dyslipidemia	6	31.6	11	12.6	19.0% (-3.0% to 41.0%)
Patients with pituitary microadenoma	6	46.2	49	75.4	29.2% (0.1% to 58.3%)
Prior medical treatment	8	44.4	50	58.1	13.7% (-11.5% to 38.9%)

CI=confidence interval
*mean + standard deviation; ^median + IQR

Adrenal crisis

There were 41 adrenal crises in nineteen patients during 457 patient-years at risk, measured in all 106 patients. This translates into 9.0 crises per 100 patient-years at risk (95% CI: 6.7-12.0). Patients had on average 2.2 crises with a range of 1 to 7 crises per patient. Time since last surgery until first crisis had a median of 2 months (IQR: 1-22 months), and time since last surgery until any crisis had a median of 20 months (IQR: 1-57 months). This means generally patients with adrenal crises had their first crisis early after their last surgery, after which they remained at risk for recurrent

crises for at least 5 years. Five patients had a crisis during the same hospital admission in which the surgery was performed, most within one week after surgery, and one patient two weeks after surgery. For most adrenal crises, patients were admitted to a regular ward only. One patient was first admitted to the intensive care and afterwards to a regular ward. Median hospital stay duration was 5 days. The average hydrocortisone replacement dose used at home (or at least advised) just before hospital admission for adrenal crisis was 30 mg/d (range 0-100 mg/d). In seven cases of adrenal crisis, the used dose was <20 mg/d. There were 29 cases of adrenal crisis with documented infection, and two with clear psychological stress. For detailed results, see Table 2.

Table 2: Adrenal crisis, (surgical) outcome, and complications.

	Adrenal crisis		**No adrenal crisis**		**Tested difference (95% CI)**
	N	**%**	**N**	**%**	
Adrenal crisis	41 crises in 457 patient-years at risk				
Number of crises per patient[#]	2.2	1-7	-	-	
Type of hospital admission					
- *Regular ward*	40	97.6	-	-	
- *Intensive care*	1	2.4	-	-	
Duration of hospital stay (days)^	5	3-9	-	-	
Hydrocortisone dose at hospital admission (mg/day)[#]	30	0-100	-	-	
Subphysiological dose of hydrocortisone replacement	7	17.1	-	-	
Infection	29	70.7	-	-	
Psychological stress	2	4.9	-	-	
Surgical outcome					
Hydrocortisone dose (mg/day) at discharge^	35	20-50	20	20-40	5 (-7.5 to 17.5)
Serum cortisol direct postoperatively (nmol/L)^°	30	20-600	40	20-100	170 (-150 to 480)
Serum cortisol 3 to 6 months postoperatively (nmol/L)^°	150	10-450	110	30-240	120 (-20 to 390)
Restoration of HPA-axis in the first year postoperatively°	1	7.1	10	14.5	7.4% (-8.4% to 23.2%)
Recurrent disease	2	10.5	12	13.8	3.3% (-12.3% to 18.9%)
Adjuvant treatment	5	26.3	18	20.7	5.6% (-15.9% to 27.1%)
Complications					
Diabetes insipidus°[+]	5	41.7	15	24.6	17.1% (-12.8% to 47.0%)
Anterior pituitary deficiency[+]	6	50.0	15	23.8	26.2% (-4.0% to 56.4%)
- *One axis*	3	25.0	11	17.4	
- *Two axes*	2	16.7	2	3.2	
- *Three axes*	1	8.3	2	3.2	

CI=confidence interval, HPA-axis=hypothalamus-pituitary-adrenal-axis
[#]mean + range, ^median + IQR, °data were missing for ≥5% of patients, [+]only for patients with transsphenoidal surgery

As there were nineteen patients with at least one adrenal crisis out of 106 patients, the risk of an adrenal crisis at baseline was 17.9%. Risk of recurrent crisis for patients with at least one adrenal crisis was eight out of nineteen (42.1%). The risk ratio of having a recurrent crisis for patients with at least one crisis was 2.3 (95% CI: 1.2-4.6) compared to having a first adrenal crisis.

Four patients experienced more than three adrenal crises (two patients with four crises, one with five crises, and one with seven crises). There is no clear pattern, which discriminates these patients from other patients in this study. All had Cushing's disease, and three were female. One had multiple adjuvant treatments (repeat transsphenoidal surgery, radiotherapy, and bilateral adrenalectomy), whereas the others only had one surgical procedure. After surgery, one patient had diabetes insipidus, one had anterior pituitary deficiency (only thyroid axis deficient), and one had both (also only thyroid axis deficient). Two patients had a cortisol stimulation test within two weeks after surgery, showing peak cortisol concentrations of 10 and 50 nmol/L. Their average hydrocortisone replacement dose before hospital admission for adrenal crisis was 30 mg/day, and in one case only, the patient received <20 mg/day (17.5 mg/day).

In Leiden, patients had 6.7 crises per 100 patient-years (95% CI: 4.5-10.0), which was 14.7 crises per 100 patient-years (95% CI: 9.7-22.3) in Berlin. In Leiden, patients were admitted to hospital for adrenal crises using lower hydrocortisone replacement doses than in Berlin (20 mg/day versus 40 mg/day), and there were more patients with a hydrocortisone replacement dose <20 mg/d at hospital admission for adrenal crisis (six cases versus one in Berlin). In five cases, hydrocortisone replacement <20 mg/d was given during a hydrocortisone withdrawal schedule, whereas in two cases, a dose <20 mg/d was already given within one month postoperatively (one in Leiden and one in Berlin), due to suspicion of persisting disease. For patients with Cushing's disease, there were 9.6 crises per 100 patient-years (95% CI: 7.0-13.3), versus 7.0 crises per 100 patient-years (95% CI: 3.6-13.6) for adrenal Cushing's syndrome. For more detailed results, see Supplemental Data 2.

The hazard ratio for patients with adrenal Cushing's syndrome compared to Cushing's disease was 0.73 (95% CI: 0.32-1.65) in a univariate Andersen-Gill model, meaning the risk for adrenal crisis was lower in patients with adrenal Cushing's syndrome. The hazard ratio for patients from Berlin compared to patients from Leiden was 2.00 (95% CI: 1.02-3.91). In a multivariate Andersen-Gill model using both etiology and research center, we found a hazard ratio for adrenal Cushing's syndrome compared to Cushing's disease of 0.59 (95% CI: 0.25-1.39) and a hazard ratio for patients from Berlin compared to patients from Leiden of 2.23 (95% CI: 1.13-4.42). Due to the low number of events, no further risk factor analyses were performed.

In Figure 1, the relation between hydrocortisone replacement dose before hospital admission for adrenal crisis and time from last surgery until adrenal crisis is shown. Patients with a short period between last surgery and adrenal crisis had higher replacement doses of hydrocortisone at the occurrence of adrenal crisis than patients with a long duration between last surgery and adrenal crisis. This means that, due to the corticosteroid withdrawal syndrome, shortly after surgery patients with Cushing's syndrome need higher replacement doses of hydrocortisone than longer after surgery to prevent adrenal crisis. Despite in general higher dosing for withdrawal complaints, patients are at risk for adrenal crisis, pointing at an increased need for hydrocortisone in these patients.

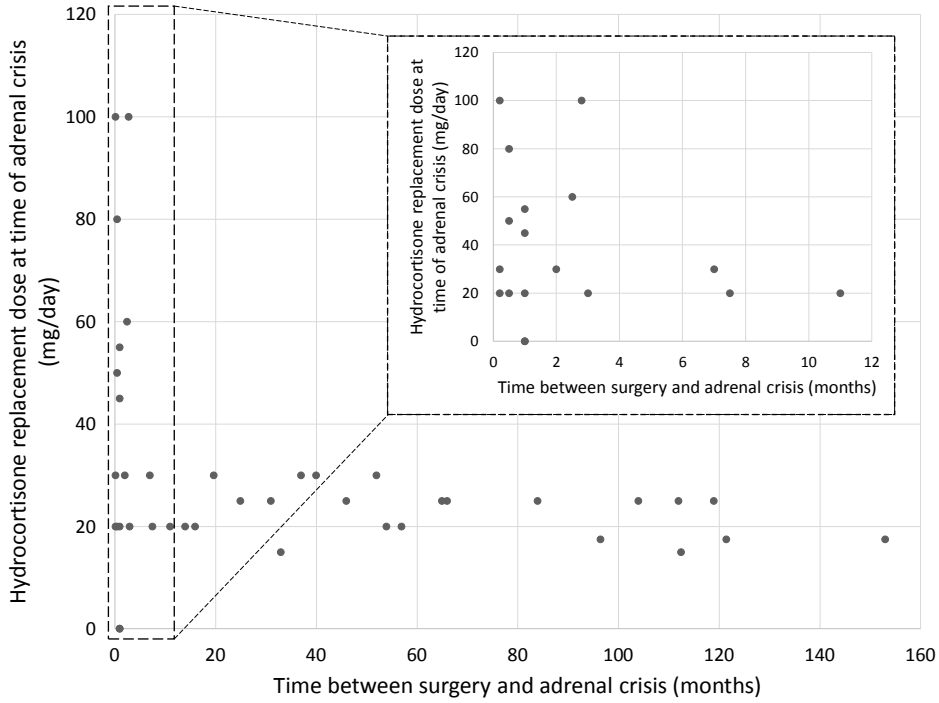

Figure 1: Relation between hydrocortisone replacement dose at time of adrenal crisis and time between last surgery and occurrence of adrenal crisis.

Stratified by time period, there were two crises in 44 patient-years at risk from 2000-2004 (5 crises per 100 patient-years, 95% CI: 1-18), fourteen crises in 142 patient-years at risk from 2005-2009 (10 crises per 100 patient-years, 95% CI: 6-16), and 25 crises in 272 patient-years at risk from 2010-2016 (9 crises per 100 patient-years, 95% CI: 6-13).

Surgical outcome and state of the HPA-axis
From the patients without adrenal crisis, twelve experienced a recurrence (14.8% out of 81 initially in remission). From the patients with at least one adrenal crisis, two experienced recurrent disease, for which they underwent repeat surgery (12.5% out of 16 initially in remission). Adrenal crises only occurred after the final treatment in each patient.

Postoperative serum cortisol concentrations were similar for patients with (median 30 nmol/L, IQR: 20-600) and without adrenal crisis (median 40 nmol/L, IQR: 20-100). There was one patient (7.1%) with restoration of the HPA-axis in the first year postoperatively who had an adrenal crisis, whereas the HPA-axis restored within a year in ten patients (14.5%) without adrenal crisis. A detailed overview of surgical outcome results can be found in Table 2, and results stratified by study center in Supplemental Data 2.

Overall survival
Five patients died in the study period, three without any adrenal crisis, and two patients with at least one adrenal crisis. Both deaths in the latter group were not related to adrenal crisis. No further mortality analyses were performed due to the small number of deaths.

Complications
Postoperatively, patients with adrenal crises had additional anterior pituitary deficiency more often than patients without any adrenal crisis (50.0% versus 23.8%), and they had a higher incidence of diabetes insipidus (41.7% versus 24.6%).

Discussion

In this exploratory study, we summarized the incidence of adrenal crisis in a population of patients with Cushing's syndrome after treatment during the postoperative period that they were adrenal insufficient. We compared patients with and without any adrenal crisis regarding potential risk factors for adrenal crisis and characteristics of Cushing's syndrome.

The incidence of adrenal crisis was 9.0 crises per 100 patient-years at risk. The risk of adrenal crisis was higher for patients from Berlin than for patients from Leiden, and higher for patients with Cushing's disease than for patients with adrenal Cushing's syndrome. First adrenal crisis occurred early after cure despite high replacement doses of hydrocortisone, and was a risk factor for recurrent crisis. No decline in incidence of adrenal crisis in time, due to better education and increased general awareness across Europe for necessity of stress instruction, was observed. Additional

pituitary deficits are more often present in patients with adrenal crisis, and may therefore be a risk factor for the occurrence of adrenal crises.

A strength of this study is the focus on adrenal crisis as primary outcome in a population of patients treated for Cushing's syndrome, including a detailed description of the underlying disease and course of the adrenal crisis. Our incidence of adrenal crisis is in line – on the high end – with the incidences reported in the literature on adrenal insufficient populations (4.1-9.3 per 100 patient-years) (2-9), and especially with one systematic review about patients with Cushing's syndrome after bilateral adrenalectomy (9.3 per 100 patient-years) (5). Our risk ratio for recurrent crisis is in line with the current literature (6).

The following study limitations need to be taken into account when interpreting our results. Due to the low absolute number of adrenal crises in our study population, the planned extensive risk factor analysis could not be performed. High percentages of loss to follow-up in both study groups, though equally divided, may have led to selection bias. As loss to follow-up could have resulted from various reasons, including both excellent health as well as very poor health status, the direction in which the results may have been biased cannot be determined. However, since our main results are in line with the literature, selection due to high loss to follow-up is unlikely to have biased our results extensively.

As should be discussed according to the STROBE guideline (22), this study is generalizable to all patients with Cushing's disease and adrenal Cushing's syndrome who are adrenal insufficient and glucocorticoid dependent after transsphenoidal pituitary surgery or adrenalectomy.

Our risk ratio for recurrent crisis indicates that certain patients are at larger risk than others to develop (multiple) adrenal crises. This may be due to decreased glucocorticoid sensitivity at the tissue level caused by polymorphisms in the glucocorticoid receptor gene (23). For these patients, the increase in hydrocortisone replacement dose during stress, or maybe even regular hydrocortisone replacement doses, may not be sufficient to prevent adrenal crisis. A further explanation may be an insufficient understanding in these patients of the instructions how to adequately anticipate with increasing the dose of hydrocortisone during stress, or insufficient compliance in increasing the hydrocortisone replacement dose. Severity of Cushing's syndrome (measured by CSI score) could not be related to occurrence of adrenal crisis. However, risk factors such as severity of Cushing's syndrome can be difficult to define, and should be studied in a large population to obtain reliable results.

The large difference in incidence of adrenal crisis between Leiden and Berlin may partially be explained by a different approach in hospital admission for patients presenting to the emergency room with signs and symptoms of early onset adrenal crisis. Patients in Leiden may preferably be treated in the emergency room, whereas patients in Berlin may rather be treated during hospital admission. On the other hand, the difference may partially be explained by different patient education strategies in the prevention of adrenal crises, possibly because in Berlin patients use higher hydrocortisone replacement doses, both at hospital discharge as well as prior to hospital admission for adrenal crisis. The difference in incidence of adrenal crisis between patients with Cushing's disease and adrenal Cushing's syndrome is small and may not represent a true difference. A difference might be explained by the different treatment methods for both etiologies. A higher risk of adrenal insufficiency and therefore adrenal crisis might be expected after adrenalectomy, which could have led to better patient education after adrenalectomy than after transsphenoidal surgery. Better awareness through education and thereby timely treatment of early symptoms of adrenal crisis could have resulted in the lower risk of adrenal crisis for patients with adrenal Cushing's syndrome.

The lack of difference in recurrence rates for Cushing's syndrome between patients with and without adrenal crisis is most likely due to selection of our patient population, as only patients with at least one period of adrenal insufficiency and glucocorticoid dependency were included in this study. Patients with adrenal crisis more often had additional pituitary hormone deficiencies than patients without any adrenal crisis, which may indicate which patients are more vulnerable, and therefore at higher risk of adrenal crisis.

The lack of improvement over time due to better education is supported by recent publications stating that patients with adrenal insufficiency are still threatened by the risk of adrenal crisis (24), that there is a clear mismatch between self-perceived understanding of adrenal insufficiency/adrenal crisis and objectively tested knowledge (9), and that definitive and timely diagnosis of adrenal crisis is often not possible before treatment needs to be initiated to prevent mortality in patients with adrenal crisis (25). Further research is needed to investigate the effects of various education methods in preventing adrenal crises and how often education should be repeated. Despite proper education, some patients may remain at higher risk of adrenal crisis due to e.g. altered glucocorticoid sensitivity (23). Furthermore, adrenal crisis occurring during hospital admission in which patients undergo surgery for Cushing's syndrome cannot be prevented merely by educating the patient. Other ways to prevent crises need to be explored, e.g. education of the endocrine nursing staff in order to recognize early stages of adrenal crisis timely. A low threshold for

contact between patient and physician could cause overtreatment, but could also result in less severe cases of adrenal crisis (26).

In conclusion, patients with a history of Cushing's disease are at risk for adrenal crisis. Adrenal crisis tends to present early after institution of cure. Those patients that have experienced adrenal crisis are at increased risk for recurrent crisis. Although some risk factors tend to point towards increased risk for adrenal crisis (e.g. additional pituitary deficiencies), we believe more outcome data are necessary to identify groups at increased risk. Further research is needed to find effective education methods for preventing adrenal crisis, and to find ways to prevent the first adrenal crisis already during the hospital stay directly after surgery.

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