THE SAHLGRENSKA ACADEMY

CUSHING'S SYNDROME IN WESTERN SWEDEN

Degree project in Medicine

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Programme in Medicine

Gothenburg, Sweden, 2018

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Abstract

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Introduction: Cushing's syndrome (CS) is a rare endocrine syndrome caused by elevated cortisol levels. Endogenous CS is most often caused by adrenocorticotrophic hormone (ACTH) secreting pituitary tumours *i.e.* Cushing's disease (CD), ACTH-secreting neuroendocrine tumours of other origin *i.e.* ectopic CS, cortisol producing adrenal adenomas, and in rarer cases adrenal carcinoma. Due to its rarity, epidemiological studies on CS are few.

Objectives: The primary aim of this study was to analyze the incidence and prevalence of endogenous CS in western Sweden. Secondary aims were to validate the diagnostic codes used for CS and to evaluate the time span from debut of symptoms to remission.

***Methods*:** Medical records from patients diagnosed with CS in the West Götaland region 2002-2017 were reviewed. In total, 234 patients had received a diagnostic code for CS. Of these, 80 patients had endogenous CS and were included in the study.

Results: The incidence of endogenous CS was 3.1 per million per year, 1.5 for CD, 0.7 for benign adrenal CS, 0.1 for adrenal carcinoma, and 0.8 for ectopic CS.

Validation of the diagnostic codes showed a sensitivity of 100% and a specificity of 70% for CD, and a sensitivity of 62% and a specificity of 93% for ectopic CS. Patients with adrenal CS were inconsistently coded with diagnostic codes of other specified CS and unspecified CS. For patients with CD, the time from debut of symptoms to remission was 30-46 months and

24 months in patients with cortisol producing adrenal adenoma.

Conclusions**:** 1) Benign adrenal CS and ectopic CS are more common than previously reported. 2) Specific diagnostic codes are needed for adrenal CS. 3) Patients with CS may have active disease for up to 4 years before adequate treatment has been provided.

Key words**:** Cushing's syndrome, incidence, prevalence, diagnostic codes, timeline

1. Introduction

1.1 Cushing's syndrome

Cushing's syndrome (CS) is a rare endocrine syndrome caused by prolonged exposure to elevated cortisol levels. Patients with CS often develop central obesity, hypertension, diabetes mellitus and osteoporosis. Depression and cognitive dysfunction are also frequently reported (1).

In order to understand the clinical features and co-morbidities of CS, the pathophysiology of the syndrome needs to be explained. Synthetization and secretion of cortisol from the adrenal cortex is regulated through adrenocorticotropic hormone (ACTH) released from the anterior pituitary gland. Similarly, ACTH is regulated by corticotropin releasing hormone (CRH) from the hypothalamus. This neuroendocrine system acts through feedback mechanisms where high plasma cortisol concentrations reduces the secretion of ACTH from the pituitary gland (1).

1.2 Aetiology

Endogenous CS is either ACTH-dependent or ACTH-independent. The most common cause of ACTH-dependent CS is Cushing's disease (CD), where elevated cortisol levels are most commonly caused by a benign ACTH-secreting pituitary adenoma, representing about 80% of all cases. ACTH-dependent CS can also originate from ACTH-secreting tumours such as small-cell lung carcinoma or other neuroendocrine tumours, collectively known as ectopic CS, accounting for about 20% of cases (2).

ACTH-independent CS is caused by autonomous cortisol secretion, where benign cortisol producing adrenal adenomas represent about 60% of cases and cortisol producing adrenal

carcinomas 40%. Finally, rarer cases of ACTH-independent CS are macronodular hyperplasia and an inherited disease called primary pigmented adrenocortical disease (PPNAD) (2).

A common cause of non-endogenous CS is iatrogenic CS due to long-term treatment with glucocorticoids. As a result of hypercortisolism, these patients present with similar clinical features as patients with endogenous CS. Furthermore, alcoholism, severe obesity and depression can induce supraphysiological cortisol production that mimics CS, a state named Pseudo CS (1).

Adrenal adenomas incidentally discovered through imaging, so called incidentalomas, are found in 1-8% of the general population. In some of these cases, a mild hypersecretion of cortisol is present, a state named subclinical CS (1). Equally, pituitary incidentalomas are common with a rate of 10% among the normal population (2).

Endogenous CS, ACTH-dependent

- Cushing's disease (CD)/ Pituitary-dependent CS/ ACTH-secreting pituitary adenoma
- Aggressive ACTH-secreting pituitary adenoma or carcinoma
- Ectopic CS (neuroendocrine tumours)

Endogenous CS, ACTH-independent

- Cortisol producing adrenal adenoma (benign)
- Macronodular adrenal hyperplasia (benign)
- Primary pigmented adrenocortical disease (PPNAD, benign)
- Cortisol producing adrenal carcinoma (malign)
- Subclinical CS (adrenal incidentaloma with pathological dexamethasone suppression test without clinical features of hypercortisolism)

Non-endogenous CS

- Iatrogenic CS (long-term glucocorticoid treatment)
- Pseudo CS (depression, alcoholism, severe obesity)

Panel 1. *Aetiologies of Cushing's syndrome (CS)*

1.3 Diagnosis

The diagnosis of CS is based on assessment of clinical features, biochemical testing and radiological imaging. Typical clinical features include rounded face, central obesity, purple striae, hypertension, glucose intolerance and psychiatric symptoms. The main biochemical analyses used to diagnose CS are urinary free cortisol, serum cortisol after dexamethasone suppression test and midnight serum or salivary cortisol (1). To determine the aetiology of CS, plasma ACTH-concentration is used to differentiate between ACTH-dependent and ACTH-independent CS. In patients with ACTH-dependent CS, MRI of the pituitary gland and sinus petrosus catheterization are usually used to differentiate between CD and ectopic CS while adrenal CT usually reveals cortisol producing adrenal adenoma in patients with ACTH-independent CS (2).

1.4 Treatments

The primary treatment of CS is almost always tumor specific surgery. For CD, surgical removal of the pituitary tumor through transsphenoidal surgery (TSS) is the most common treatment and unilateral adrenalectomy for unilateral cortisol producing adrenal adenoma or carcinoma (1). Postoperatively, remission is confirmed by low serum cortisol concentrations (2).

Medical therapies, usually with steroidogenesis inhibitors such as Ketoconazole and Metyrapone, are often used to lower cortisol levels prior to surgery. Pituitary radiotherapy is also a treatment option, mainly in patients who do not achieve remission after TSS (2). After TSS and especially radiotherapy, the patient has a risk of developing hypopituitarism (growth hormone deficiency, hypogonadism and hypothyroidism). In patients who do not achieve remission after treatment with surgery or radiation, bilateral adrenalectomy is the treatment of

choice. Surgical removal of both adrenal glands is always curative for ACTH-dependent CS, but results in life-long glucocorticoid and mineralocorticoid deficiency (1). After bilateral adrenalectomy in patients with CD, a concern is that the remaining pituitary tumor continues to grow and secrete large amounts of ACTH that results in hyperpigmentation, a state called Nelson's syndrome (2).

1.5 Morbidity and mortality

Initially described by Harvey Cushing, CS is associated with increased morbidity and mortality (3). Today, patients with incompletely treated CS sill have up to five-hold increased mortality rate compared to the general population (4). However, mortality in patients in long-term remission is still debated. In a study including patients with CS of all aetiologies, mortality was reported to be similar as compared to the general population (5). In another study on CD, mortality was significantly increased (6). This difference is probably explained by the heterogeneity of the patients, duration of hypercortisolism, treatment methods and definition of remission.

Despite clinical and biochemical long-term remission, co-morbidities remain high in patients with CS. Patients with CD in long-term remission maintain a high cardiovascular risk (7) and similarly, patients with CD or adrenal CS have an increased risk of myocardial infarction, stroke and venous thromboembolism (8). Duration of hypercortisolism before CS diagnosis may predict increased mortality (9), emphasizing the importance of early recognition and treatment to reduce symptoms, co-morbidities and mortality.

1.6 Epidemiology

Due to its rarity, and heterogeneity, studies on CS are few. In particular epidemiological studies on the incidence and prevalence of CS. A Danish study from 2001 reported an incidence of 1.2 to 1.7 per million per year for CD, 0.6 per million per year for cortisol producing adrenal adenoma and 0.2 per million per year for adrenal carcinoma (4). A study from New Zeeland, published in 2011, estimated the prevalence of CS to be 79 cases per million and the incidence to be 1.8 per million per year, excluding adrenal carcinoma and malignant ectopic CS (10). In 2014, a study from the US estimated the total incidence of CS to be 49 cases per million per year and for only CD, nearly 8 cases per million per year (11), a considerably higher incidence rate than previously reported. These findings suggest that data on incidence and prevalence of endogenous CS needs further evaluation.

The primary aim of this study was to analyze the incidence and prevalence of endogenous CS in western Sweden from 2002 to 2017. Secondary aims were to validate the diagnostic codes used for CS and to evaluate the time span from debut of symptoms to recognition, diagnosis, treatment and remission for patients with CS.

2. Specific scientific questions

- What is the incidence and prevalence of endogenous CS in West Götaland Region during the period 2002-2017?
- How many patients registered with diagnostic ICD-10 codes used for CS actually have the syndrome?
- What is the time span from debut of symptoms through recognition, diagnosis, and treatment, to remission in patients with endogenous CS?

3. Methods

3.1 Study design and description of the area of coverage

This was a retrospective chart review of all patients diagnosed with CS in the West Götaland Region, Sweden during the period from 2002 to 2017. At the end of the study (December 31, 2017), the West Götaland Region had a population of 1 690 782 (National database of statistics, Sweden, SCB).

There are seven hospitals in the West Götaland Region; the Sahlgrenska University Hospital in Göteborg, with departments of endocrinology, endocrine surgery and neurosurgery, and six local hospitals with endocrine departments. All patients with suspected CS in West Götaland Region are referred to the Sahlgrenska University Hospital for evaluation and treatment.

3.2 Identification of patients

All hospital visits in Sweden are coded in a diagnosis-related group (DRG) registry.

To identify patients with CS, a search in the DRG-registry at the Sahlgrenska University Hospital was performed for the following ICD-10 codes: Pituitary-dependent CS (E24.0), Nelson's syndrome (E24.1), Iatrogenic CS (E24.2), Ectopic ACTH-syndrome (E24.3), Alcohol-induced CS (E24.4), Other specified CS (E24.8) and Unspecified CS (E24.9).

Patients excluded from the analysis were; a) patients with endogenous CS not living in the West Götaland Region at the time of diagnosis, *i.e*. patients from other countries or other regions in Sweden, b) patients who, after review of clinical, biochemical and imaging data, did not have the diagnosis of endogenous CS confirmed, including patients with iatrogenic CS and pseudo CS, and c) patients who had received CS diagnosis in the West Götaland Region

before 2002. The last group was however included in the calculation of prevalence rates.

3.3 Collection and validation of data

Medical records for identified patients at all hospitals in the West Götaland Region (including the hospitals in Göteborg, Borås, Trollhättan, Skövde, Uddevalla, Alingsås and Lidköping), available through the electronic journal database at the Sahlgrenska University Hospital, were reviewed.

A Microsoft Excel file, including pre-defined variables, was created to collect patient data in a structured manner. In patients where exact dates of biochemical testing, diagnosis, treatments, visits and other variables were missing, the dates were roughly estimated to month and year. For some variables, data were unknown or missing. For these variables, calculations were based on the available data.

3.3.1 Validation of the CS diagnosis

Clinical features, biochemical data, imaging and histopathological diagnosis of all patients diagnosed with CS in the West Götaland Region from 2002 to 2017 were evaluated by the authors through chart review to validate the diagnosis of CS.

Biochemical data from patients with ACTH-independent CS (together with imaging results) were usually sufficient to confirm aetiology. However, in patients with ACTH-dependent CS, biochemical testing (and imaging) were rarely conclusive for a specific aetiology, *i.e.* ACTH-secreting pituitary adenoma or ectopic CS. In most cases, sinus petrosus catheterization together with histopathological examination, were the cardinal methods to determine aetiology. Patients with adrenal incidentalomas and pathological dexamethasone suppression test, without typical clinical features of hypercortisolism, were classified as subclinical CS.

Sensitivity and specificity of the diagnostic codes for CD (E24.0), Iatrogenic CS (E24.2) and Ectopic CS (E24.3) were calculated, based on how many patients with endogenous CS who had received an adequate code and how many patients without endogenous CS had received an inappropriate diagnostic code.

3.3.2 Referral and first visit

The first visit at the referring doctor who suspected CS was reviewed, as well as the first visit at the Sahlgrenska University Hospital, usually the first visit at the department of endocrinology.

3.3.3 Duration of symptoms and clinical features

Duration of symptoms (months) was estimated through chart review. This estimation was most often based on the patients' own description of debut of characteristic symptoms of CS such as weight gain and fatigue. Presence of and/or treatment for hypertension and diabetes at the time of CS diagnosis were also recorded.

3.3.4 Biochemical testing

Results from the following biochemical tests were recorded; a) 1-3 measurements of 24-hr urinary free cortisol (UFC), b) serum cortisol after low-dose (1 mg) overnight dexamethasone, c) serum cortisol after 48-hr (0.5 mg x 4 for 48 hrs) dexamethasone suppression, d) morning (8 AM) plasma ACTH-concentrations and e) midnight serum cortisol. The upper limit of the normal (ULN) for UFC was also noted, since assays, and thereby normal reference ranges, were different between hospitals and/or changed during the study period.

In some patients, all of the above mentioned biochemical tests were performed, but in many cases, not all tests were required for diagnosis. For example, in patients with a typical clinical

picture and very high UFC, a dexamethasone suppression test did not add any further information to the diagnostic process.

3.3.5 Imaging

In patients with ACTH-dependent CS, results of conventional pituitary MRI, dynamic pituitary MRI, CT abdomen and CT thorax were collected. In patients with ACTH-independent CS, results of CT adrenal were recorded.

3.3.6 Invasive testing

Among most patients with ACTH-dependent CS, the aetiology could not be fully confirmed until sinus petrosus catheterization had been performed, indicating localization of the tumor. Adrenal vein catheterization was performed in rare cases of CS with bilateral adrenal lesions on CT, where cortisol and aldosterone concentrations were used to determine lateralization.

Biochemical testing

- **Urinary free cortisol** UFC, 24-hr collection (elevated levels indicates hypercortisolism)
- **Dexamethasone suppression test** overnight/48-hr (no suppression indicates endogenous CS)
- **Midnight serum cortisol** (elevated levels indicate no 24-hr cortisol variation)
- **Morning plasma ACTH** (elevated levels indicate ACTH-dependent CS)

Imaging

- **Pituitary MRI** (shows pituitary tumor)
- **Dynamic pituitary MRI** (dynamic sessions shows invisible pituitary tumor)
- **CT adrenal** (shows adrenal tumor)

Invasive testing

- **Sinus petrosus catheterization** (indicates pituitary or ectopic origin of tumor in ACTH-dependent CS)
- **Adrenal vein catheterization** (indicates lateralization in patients with bilateral adrenal lesions)

Panel 2. *The diagnostic process of Cushing's syndrome (CS)*

3.3.7 Aetiology

The diagnostic process of CS is known to be complex and includes evaluation of clinical features, biochemical tests, invasive tests and imaging as explained above. In this study, diagnosis and aetiology was usually determined by an endocrinologist in accordance to recommended diagnostic criteria at the time of diagnosis (12).

The aetiology of CS in the patients of the current study were confirmed by authors through chart review. Benign ACTH-secreting pituitary adenomas and aggressive ACTH-secreting pituitary adenomas or carcinomas were classified as CD. ACTH-secreting tumors originating from outside of the pituitary region were classified as ectopic CS. Benign cortisol producing adrenal adenoma, PPNAD and macronodular hyperplasia were classified as benign adrenal CS and malignant cortisol producing adrenal tumors as adrenal carcinoma.

3.3.8 Treatments

All treatments that the patients had received were recorded as well as curative treatment. Curative treatment was defined as TSS or unilateral adrenalectomy with low cortisol levels postoperatively, or bilateral adrenalectomy. Pituitary radiotherapy was considered curative when the patients subsequently developed normocortisolemia or adrenal insufficiency.

3.3.9 Remission and recurrence

Remission status post operatively was determined through chart review and based on one or more of the following criteria; 1) Low cortisol level after TSS or unilateral adrenalectomy 2) Resolution of clinical symptoms and features after treatment 3) Normalization of UFC 4) Normalization of cortisol 24-hr variation 5) Adequate suppression of cortisol after dexamethasone suppression test 6) Adrenal insufficiency and/or glucocorticoid dependency 7)

Bilateral adrenalectomy. Remission status at the last clinical visit was categorized in a similar manner.

Date of remission was set to the date of the curative treatment when the patient achieved remission, for example when a patient had low cortisol levels after the first TSS. Recurrence of CS was defined as clinical and biochemical signs of CS in patients after previously been considered in remission.

3.3.10 Histopathology

Histopathological reports from the tumor tissue that was removed during surgery were reviewed. In patients with CD, the immunohistological findings were reviewed as well.

3.3.11 Death

Date to death was recorded and available in all patients who had died.

3.4 Statistics

3.4.1 Incidence and prevalence

The incidence rates of endogenous CS in West Götaland Region were calculated by dividing the total number of patients diagnosed with CS between 2002 and 2017 with the mean population rate of West Götaland region from 2002 through 2017 multiplied by 16 (the number of years included in the study). According to the national database of statistics in Sweden (SCB) the population of West Götaland Region was 1 500 857 at December 31, 2001 and 1 690 782 at December 31, 2017. Calculations on incidence were performed separately for CD, benign adrenal CS (including cortisol producing adrenal adenoma, macronodular hyperplasia and PPNAD), cortisol producing adrenal carcinoma and ectopic CS.

Prevalence was estimated by dividing the number of patients diagnosed with CS between 2002 and 2017, as well patients diagnosed with CS before 2002, who were alive at the end of the study, with the population rate of West Götaland region at December 31, 2017. Prevalence rates were calculated separately for CD, benign adrenal CS, adrenal carcinoma and ectopic CS.

3.4.2 Timeline

To evaluate the time span from debut of symptoms to recognition, diagnosis, treatment and remission, a timeline was created to visualize the time from debut of symptoms to remission for patients with endogenous CS. Calculations were made separately for CD, benign adrenal CS, adrenal carcinoma and ectopic CS.

Time-differences between dates for the following variables were calculated: the first visit at referral doctor to diagnosis CS, diagnosis CS to the first attempted curative treatment, and the first attempted curative treatment to remission.

3.4.3 Statistical methods

Descriptive data are presented as mean ± SD or median (range; interquartile range). For comparison between two groups, unpaired T-test was used for normally distributed data and Mann-Whitney U-test for non-normally distributed data. For proportions, Pearson Chi-square or Fishers exact test were used. A P-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 25.

4. Ethics

The ethical committee of the University of Gothenburg, Göteborg, Sweden approved the study. The study was conducted according to the Declaration of Helsinki.

5. Results

5.1 Validation of the CS diagnosis

By a search for the diagnostic codes of CS in the DRG-registry, registered between 2002 and 2017 in the West Götaland Region, 234 patients were identified (Figure 1).

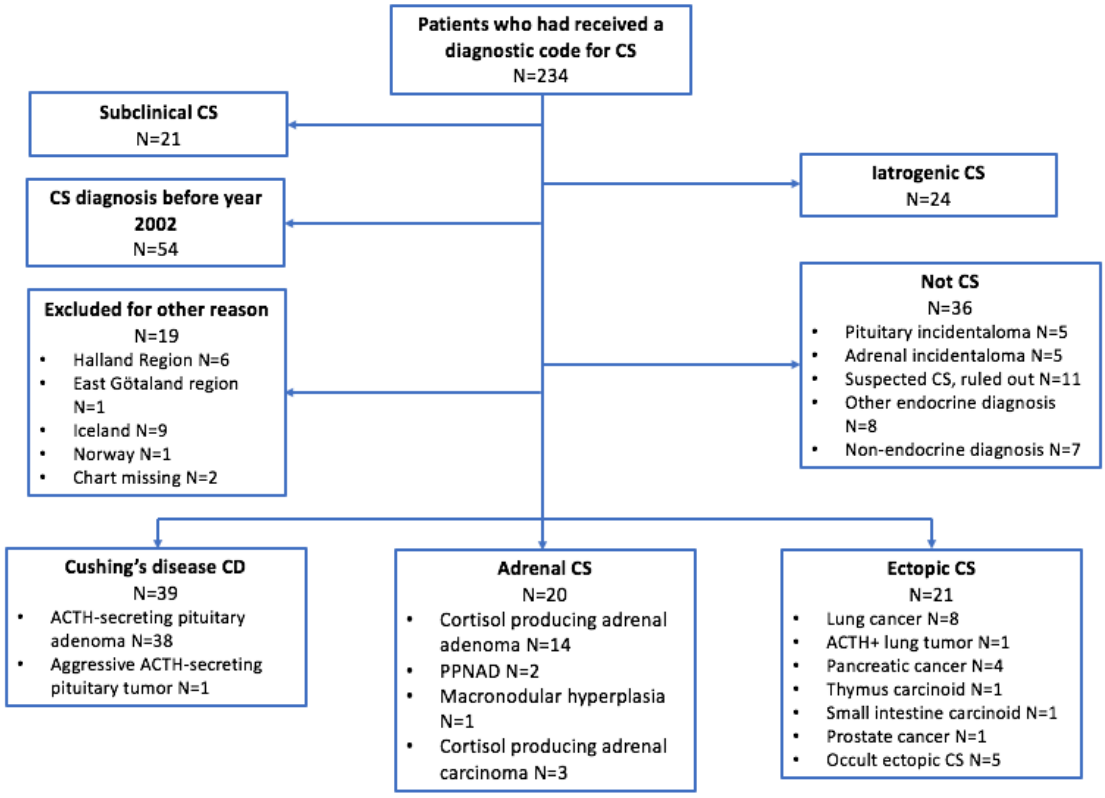

Figure 1. *Identified patients who had received a diagnostic code for Cushing's syndrome (CS)*

In total, 38 patients (26 women and 12 men) had ACTH-secreting pituitary adenoma and one female patient had an aggressive ACTH-secreting pituitary tumour. Thus, 39 patients were diagnosed with CD. The aetiology was confirmed through histopathological diagnosis in 30 (77%) of the patients with ACTH-secreting pituitary adenoma and in the patient with aggressive ACTH-secreting pituitary tumour. In four patients with CD the histopathological examination showed normal pituitary tissue (three of these patients were in remission

postoperatively and one patient was not in remission) and in five patients, histopathological data was missing.

Sinus petrosus catheterization was conducted in 37 patients and confirmed CD in 31 patients and ectopic CS in six patients. Six patients with CD who were not investigated with sinus petrosus catheterization had a pituitary macroadenoma (>8mm) and data were missing for two patients. Thus, in 36 of 39 patients with CD (92%), the diagnosis was confirmed with histopathological examination and/or sinus petrosus catheterization.

All 39 patients with CD had received the diagnostic code for pituitary-dependent CS, E24.0 (Figure 2). Seventeen patients who had received E24.0 did not have CD. Thus, the sensitivity and specificity of the diagnostic code were 100% and 70%, respectively.

Twenty-one patients were diagnosed with ectopic CS (13 women and 8 men). In nine patients, the primary tumour was localized in the lungs. Four patients had histologically confirmed small cell lung carcinoma with metastases. Four had had received the diagnosis lung cancer (of which three also had liver metastases) based on imaging, three of these without histopathological diagnosis and one with histologically confirmed brain metastases from neuroendocrine carcinoma. One patient had a histologically confirmed ACTH-positive neuroendocrine lung tumour. In four patients with ectopic CS, the primary tumour was localized in the pancreas of which all had histologically confirmed pancreatic neuroendocrine cancer with liver metastases. One patient had a histologically confirmed thymus carcinoid with skeletal metastases, one patient had a histologically confirmed small intestine carcinoid with multiple metastases and in one patient with spread metastases, the primary tumour was assumed to be prostate cancer. In five patients, the localization of the ACTH-secreting tumour was unknown despite biochemical, imaging and histopathological examination (occult ectopic

CS). Two of these five patients had metastatic disease proven through imaging and three had performed sinus petrosus catheterization that confirmed the diagnosis.

Thirteen (62%) of the patients with ectopic CS received the correct diagnostic code E24.3 for ectopic CS, two patients received E24.0 (Pituitary-dependent CS), three patients E24.8 (Other specified CS) and three patients E24.9 (Unspecified CS). One patient who had received E24.3 did not have ectopic CS. Thus, the sensitivity and specificity of the diagnostic code were 62% and 93%, respectively.

Of 17 patients with benign adrenal CS, 14 had a unilateral cortisol producing adrenal adenoma (13 women and one man), histologically confirmed in 13 patients (missing for one patient). In one patient with bilateral adrenal lesions on CT, unilateral cortisol producing adrenal adenoma was confirmed through adrenal vein catheterization. Two female patients had histologically confirmed PPNAD and one male patient had histologically confirmed macronodular hyperplasia. Bilateral cortisol production in the patients with PPNAD and macronodular hyperplasia were confirmed by adrenal vein catheterization. Thus, in 16 of 17 patients with benign adrenal CS (94%), the diagnosis was confirmed through histopathological examination and/or adrenal vein catheterization.

The diagnostic codes used for the patients with benign adrenal adenoma were E24.8 (Other specified CS, N=7) and E24.9 (Unspecified CS, N=7). One of the patients with PPNAD received the diagnostic code E24.8 (Other specified CS) and the other received E24.9 (Unspecified CS). The patient with macronodular hyperplasia received E24.9 (Unspecified CS).

Three patients had histologically confirmed adrenocortical cancer with metastases. The diagnostic codes used were E24.8 (Other specified CS, N=1) and E24.9 (Unspecified CS,

N=1). The third patient, known by the authors, had not received a diagnostic code for CS. All three patients with cortisol producing adrenal carcinoma received the diagnostic code for adrenocortical cancer, C74.0.

Pituitary dependent CS E24.0	**Nelson's syndrome** E24.1	**Iatrogenic CS** E24.2	**Ectopic CS** E24.3	**Alcohol induced CS** E24.4	**Other specified CS** E24.8	**Unspecified CS** E24.9
Cushings' disease N=39	Fructose intolerance N=1	Iatrogenic CS N=19	Ectopic CS N=13	Pseudo CS, alcohol induced N=1	Adrenal adenoma N=7	Adrenal adenoma N=7
Ectopic CS N=2		Secondary adrenal insufficency N=1	Hypophysitis N=1		PPNAD N=1	PPNAD N=1
Iatrogenic CS N=1					Adrenal carcinoma N=1	Macronodular hyperplasia N=1
Pituitary incidentaloma N=3					Ectopic CS N=3	Adrenal carcinoma N=1
Adrenal incidentaloma N=1					Iatrogenic CS N=2	Ectopic CS N=3
Pseudo CS N=2					Subclinical CS N=8	Iatrogenic CS N=2
Craniopharyngeoma N=1					Pituitary incidentaloma N=1	Subclinical CS N=13
Glycogenosis N=3					Chest pain N=1	Pituitary incidentaloma N=1
Glucocorticoid resistance N=1					Femur fracture N=1	Adrenal incidentaloma N=4
Acromegaly N=1					Carpal tunnel syndrome N=1	GH-deficiency N=1
Prolactinoma N=1						
Conn's syndrome N=1						

Figure 2. *Validation of the diagnostic codes for Cushing's syndrome (CS)*

Twenty-four patients had iatrogenic CS due to long-term treatment with glucocorticoids. Underlying diseases of these patients were brain tumors, rheumatoid arthritis, inflammatory bowel disease, asthma and other conditions treated with glucocorticoids. Nineteen of the patients with iatrogenic CS received the adequate diagnostic code of E24.2, two received E24.8 (Other specified CS), one E24.0 (Pituitary-dependent CS) and two E24.9 (Unspecified CS). One patient who had received E24.2 did not have iatrogenic CS. Thus, the sensitivity and specificity of the diagnostic code were 79% and 95%, respectively.

Twenty-one patients had adrenal incidentalomas with subclinical CS, of which eight underwent unilateral adrenalectomy and five received medical therapy. The diagnostic codes

used for patients with subclinical CS were E24.8 (Other specified CS, N=8) and E24.9 (Unspecified CS, N=13)

Ten patients were initially suspected to have CS. In five, CS was ruled out after clinical and biochemical evaluation, three had pseudo CS; one due to high alcohol intake, one from depression and one from eating disorder. Furthermore, two patients had a suspected CS but refused evaluation and one patient with suspected CS was never evaluated for an unknown reason. Finally, eight patients had other endocrine diagnoses and seven had non-endocrine diagnoses (Figure 3).

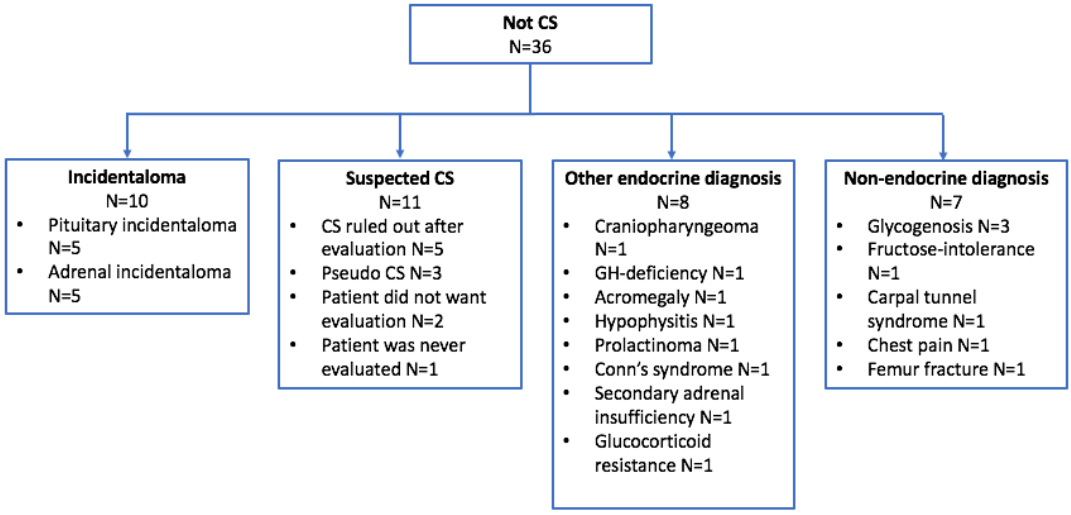

Figure 3. *Identified patients who did not have Cushing's syndrome (CS)*

Of the 234 identified patients who had received a diagnostic code for CS, 17 patients with endogenous CS were excluded for not living in the West Götaland region and charts for two patients were missing. Additionally, 54 patients had received a diagnosis for endogenous CS before 2002 (Figure 1).

5.2 Demographics

After review of clinical, biochemical, imaging and histopathological data, 80 patients (56 women and 24 men) fulfilled the inclusion criteria. In total, 60 patients had ACTH-dependent CS; 39 patients had CD (38 patients had a benign pituitary adenoma and one patient an aggressive ACTH-secreting pituitary tumor) and 21 patients had ectopic CS.

Twenty patients had ACTH-independent CS; 14 patients had cortisol producing adrenal adenoma, two patients had PPNAD, one had macronodular hyperplasia and three had cortisol producing adrenal carcinoma. Patient demographics and causes of endogenous CS are shown in Table 1.

Table 1. *Patient demographics and aetiology of endogenous Cushing's syndrome (CS)*

	All	**Cushing's disease**	**Benign adrenal CS**	**Adrenal carcinoma**	**Ectopic CS**
	N=80	N=39	N=17	N=3	N=21
Mean age (SD)	50 (18)	48 (17)	44 (16)	29, 43, 52*	59 (18)
Female gender	56 (70)	27 (69)	15 (88)	1 (33)	13 (62)
Hypertension at diagnosis	59 (74)	28 (72)	12 (71)	2 (67)	17 (81)
Diabetes at diagnosis	26 (33)	10 (26)	5 (29)	0 (0)	11 (52)

Data are presented as mean (SD) and N (%).
*Ages of patients.

The mean age at diagnosis for endogenous CS was 50 years (SD 18), 47 years for women (SD 18) and 57 years for men (SD 16). For CD, mean age at diagnosis was 48 years (SD 17), for benign adrenal CS 44 years (SD 16) and for ectopic CS 59 years (SD 18). Patients with ectopic CS were significantly older at diagnosis compared to patients with CD (P=0.028) and patients with benign adrenal CS (P=0.014). The three patients with cortisol producing adrenal carcinoma were 29, 43 and 52 years old at diagnosis. Age distribution for all patients with endogenous CS are shown in Figure 4.

Of all patients with endogenous CS, 56 (70%) were women. For CD, 27 (69%) patients were women, for benign adrenal CS 15 (88%) and for ectopic CS 13 (62%). Among the three patients with adrenal carcinoma, one was a woman (33%). Of the 80 patients with endogenous CS, 59 (74%) had hypertension at diagnosis CS and 26 (33%) had diabetes mellitus at diagnosis (Table 1).

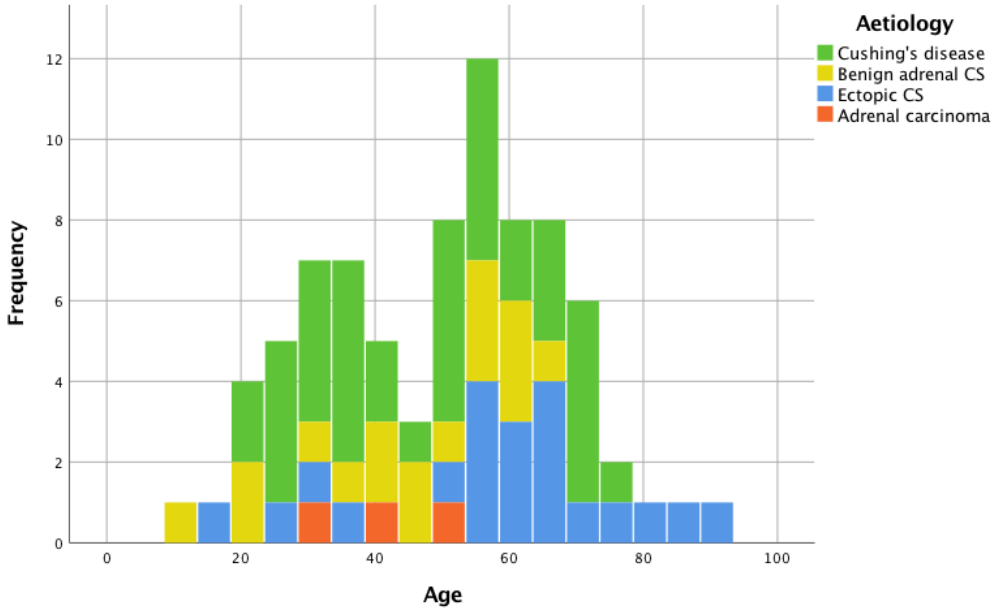

Figure 4. *Age distribution for patients with endogenous Cushing's syndrome (CS)*

5.3 Incidence and prevalence

The total incidence of endogenous CS in the West Götaland region between 2002 to 2017 was 3.1 per million per year. The number of new cases with endogenous CS varied over the years, the lowest rates were in 2003 when only one patient was diagnosed with benign adrenal CS compared to 2013 when 11 new cases of endogenous CS were reported (Figure 5).

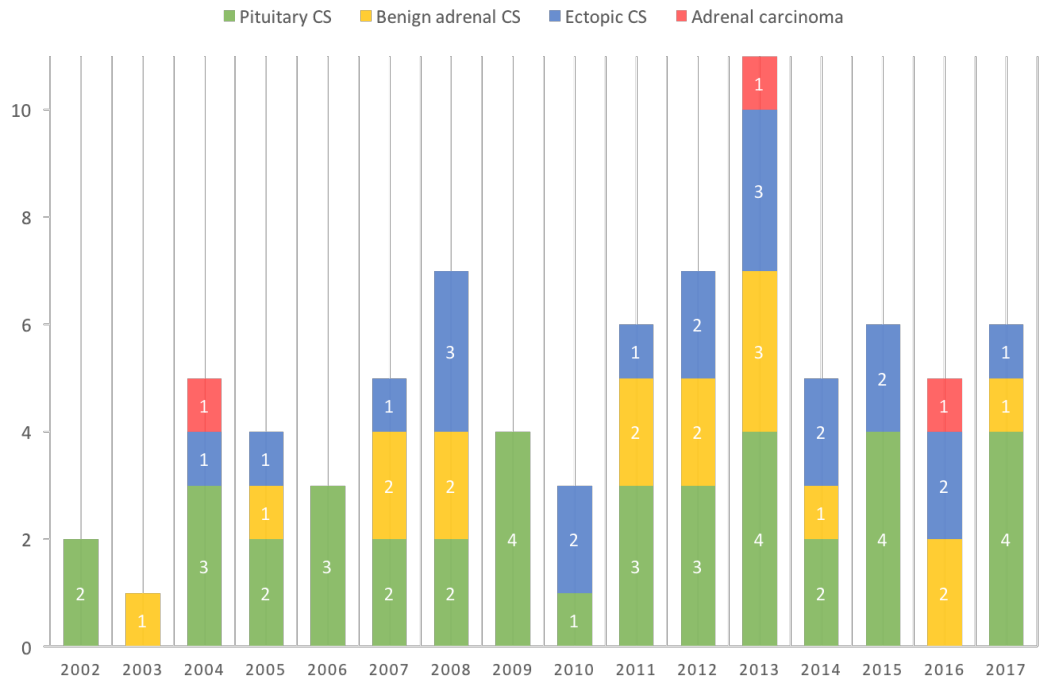

Figure 5. *Annual incidence of endogenous Cushing's syndrome (CS) in the West Götaland Region 2002-2017*

At the end of the study, five of 54 patients who were diagnosed with endogenous CS before 2002 were not living in the West Götaland region and ten had died. Of the 80 patients diagnosed with CS between 2002-2017, four patients were not living in the West Götaland region and 22 patients had died at the end of the study (18 patients with ectopic CS, 2 patients with adrenal carcinoma and 2 patients with CD). In total, 93 patients were included in the prevalence calculations, 54 patients diagnosed between 2002 and 2017 and 39 diagnosed before 2002 (24 patients with CD and 15 with benign adrenal CS). Thus, the prevalence of endogenous CS in the West Götaland region at the end of the study was 57 per million.

Incidence rate for CD during the study period was 1.5 per million per year and the total prevalence was 36 per million. For benign adrenal CS (including cortisol producing adrenal adenoma, PPNAD and macronodular hyperplasia) the incidence was 0.7 per million per year and the prevalence was 19 per million. For cortisol producing adrenal carcinoma, the

incidence was 0.1 per million per year and the prevalence was 0.6 per million. The incidence rate for ectopic CS was 0.8 per million per year and the prevalence was 1.8 per million (Table 2).

Table 2. *Incidence and prevalence of endogenous Cushing's syndrome (CS) in the West Götaland region*

	All	**Cushing's disease**	**Benign adrenal CS**	**Adrenal carcinoma**	**Ectopic CS**
	N=80	N=39	N=17	N=3	N=21
Incidence (/million/year)	3.1	1.5	0.7	0.1	0.8
Prevalence (/million)	57.4	36	19	0.6	1.8

5.4 Timeline

A timeline was created to visualize the time span for the patients from debut of symptoms through first visit at the referral doctor, diagnosis, first treatment and curative treatment, to remission. For one patient with CD, dates for the first visit at referral doctor and diagnosis were missing and the patient was excluded from the calculations. Data from the timeline analysis is shown in Table 3.

Table 3. *Timeline data for patients with endogenous Cushing's syndrome (CS)*

	All	**Women**	**Men**	**Cushing's disease**	**Benign adrenal CS**	**Adrenal carcinoma**	**Ectopic CS**	**P0**	**P1**	**P2**	**P3**
	N=79	N=55	N=24	N=38	N=17	N=3	N=21				
Duration of symptoms (months)	12 (0-120) [2-30]	24* (0-120) [12-36]	21* (0-60) [6-48]	24 (0-120) [12-48]	18 (0-108) [7-30]	0, 5, 7	1 (0-30) [0-5]	0.509	<0.001	<0.001	0.251
First visit to diagnosis CS (days)	56 (0-708) [15-112]	76* (0-708) [34-166]	59* (3-613) [23-166]	69 (0-708) [29-120]	100 (7-613) [65-190]	0, 7, 47	14 (0-374) [6-47]	0.324	0.003	<0.001	0.092
Diagnosis CS to first treatment (days)		106* (1-359) [58-184]	118* (1-576) [101-183]	118 (1-359) [81-212]	83 (19-576) [58-116]	0, 10, 12		0.283			0.090
First treatment to remission (days)				464 (236-2055) [248-1585]							
Remission at last visit (%)				92	100	0	14				
Relapse (N)	9	5	4	5	0	1	3				
Death (N)	22	12	10	2	0	2	18				

Data are median (range) and interquartile [range]
* Analysis is performed on patients with CD and benign adrenal CS, women (N=41) and men (N=14)
P0: Mann-Whitney U-test, women compared to men
P1: Mann-Whitney U-test, CD compared to ectopic CS
P2: Mann-Whitney U-test, benign adrenal CS compared to ectopic CS
P3: Mann-Whitney U-test, CD compared to benign adrenal CS

5.4.1 Duration of symptoms

The duration of symptoms prior to diagnosis was 12 months (range 0-120, interquartile range 2-30) for all endogenous CS. For CD, the duration of symptoms was 24 months (range 0-120, interquartile range 12-48), for benign adrenal CS 18 months (range 0-108, interquartile range 7-30) and for ectopic CS one month (range 0-30, interquartile range 0-5). The three patients with cortisol producing adrenal carcinoma had duration of symptoms of 0, 5 and 7 months. The duration of symptoms in patients with CD and benign adrenal CS was significantly longer compared to patients with ectopic CS ($P<0.001$). No significant difference in duration of symptoms was found between CD and benign adrenal CS ($P=0.251$).

In patients with CD or benign adrenal CS, the duration of symptoms were 24 months for women (range 0-120, interquartile range 12-36) and 21 months for men (range 0-60, interquartile range 6-48). There was no significant difference between women and men ($P=0.509$).

5.4.2 Time from first visit at referral doctor to diagnosis CS

The diagnosis CS was already established in 16 patients with endogenous CS at some of the six local hospitals in West Götaland region when admitted to the department of endocrinology at the Sahlgrenska University Hospital.

The time from first visit at referral doctor to confirmed diagnosis of CS for all endogenous CS was 56 days (range 0-708, interquartile range 15-112). For CD, 69 days (range 0-708, interquartile range 29-120), benign adrenal CS, 100 days (range 7-613, interquartile range 65-

190), and ectopic CS 14 days (range 0-374, interquartile range 6-47). The time from first visit to diagnosis CS in the patients with adrenal carcinoma was 0, 7 and 47 days. The time from first visit to diagnosis of CD and benign adrenal CS was significantly longer compared to diagnosis of ectopic CS (P=0.003 and P<0.001, respectively). There was no significant difference between CD and benign adrenal CS (P=0.092).

In patients with CD or benign adrenal CS, the time to diagnosis were 76 days for women (range 0-708, interquartile range 34-166) and 59 days for men (range 3-613, interquartile range 23-166; P=0.324).

5.4.3 Time from diagnosis CS to first treatment

First treatment was defined as the first attempted curative treatment, for example TSS or unilateral adrenalectomy. Medical therapy was given preoperatively in 54 of the 80 patients to reduce cortisol levels, but was not considered a curative treatment.

For CD, TSS was performed in 36 of the 38 patients. One patient had an inoperable ACTH-secreting pituitary adenoma and received medical therapy and radiotherapy. One patient with CD died before the first attempted curative treatment and was excluded from further calculations. The time from diagnosis of CD (N=37) to first attempted curative treatment was 118 days (range 1-359, interquartile range 81-212).

For unilateral cortisol producing adrenal adenoma, unilateral adrenalectomy was performed in all 14 patients. Both patients with PPNAD and the patient with macronodular hyperplasia had bilateral adrenalectomy. For the 17 patients with benign adrenal CS, the time from diagnosis to first treatment was 83 days (range 19-576, interquartile range 58-116). The time from diagnosis to first treatment did not differ significantly between CD and benign adrenal CS (P=0.090).

The time from diagnosis to first attempted curative treatment for CD and benign adrenal CS was 106 days for women (range 1-359, interquartile range 58-184) and 118 days for men (range 1-576, interquartile range 101-183; P=0.283).

In the 21 patients with ectopic CS, various treatments were given. Eleven patients had medical therapy as the sole treatment, three patients had medical therapy and oncological treatment (including tumor specific surgery, chemotherapy and/or radiotherapy), four patients had medical therapy, oncological treatment and bilateral adrenalectomy and two patients had medical therapy and bilateral adrenalectomy. Pulmonary lobectomy was performed in one patient with ACTH-positive neuroendocrine lung tumor. For ectopic CS, the median time from diagnosis to first attempted curative treatment was not calculated because most patients had received various medical and/or oncological treatments before diagnosis CS, and the treatments were rarely curative.

All three patients with adrenal carcinoma received unilateral adrenalectomy, tumor specific therapy for metastases, various medical therapies and oncological treatments. For adrenal carcinoma, the time from diagnosis to first treatment was 0, 10 and 12 days. However, similar to ectopic CS, the given treatments for patients with adrenal carcinoma were rarely curative.

5.4.4 Time from first treatment to remission

In the 38 patients with CD, 35 patients (92%) were in remission at last visit. For one patient, remission status was uncertain and two patients with CD had died before achieving remission. Of the 35 patients with CD who were in remission at the last clinical visit, 24 (69%) had achieved remission after the first TSS and one after pituitary radiotherapy and medical therapy (Figure 6). Ten (29%) of the patients required additional treatments in various combinations. Four patients had a second TSS and one patient had a second TSS and pituitary radiotherapy. Two patients required pituitary radiotherapy after the first TSS and one patient

had bilateral adrenalectomy after the first TSS. Finally, one patient required three TSS, pituitary radiotherapy and bilateral adrenalectomy to achieve remission. The patient with aggressive ACTH-secreting pituitary tumor achieved remission 9 months following diagnosis, after receiving medical therapy, TSS, pituitary radiotherapy and chemotherapy.

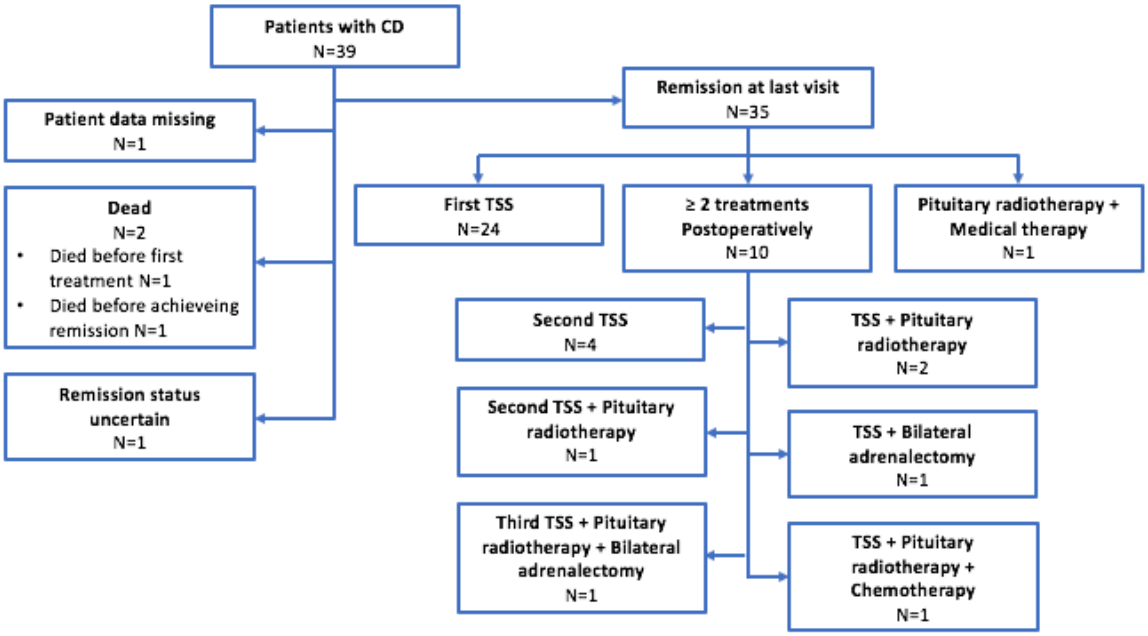

Figure 6. *Treatments and remission status in patients with Cushing's disease (CD). TSS = Trans sphenoidal surgery.*

The time from first treatment to remission in CD patients who were not in remission after the first attempted curative treatment and did not have recurrent disease (N=5) was 464 days (range 236-2055, interquartile range 248-1585).

All 14 patients with cortisol producing adrenal adenoma achieved remission after unilateral adrenalectomy. Both patients with PPNAD and the patient with macronodular hyperplasia achieved remission after bilateral adrenalectomy. None of the three patients with cortisol producing adrenal carcinoma were in remission post-operatively or at the last clinical visit.

Only three (14%) of the 21 patients with ectopic CS achieved remission; one patient with a ACTH-positive neuroendocrine lung tumor who achieved remission after pulmonary

lobectomy and two patients with unknown primary ACTH-secreting tumor who achieved remission after bilateral adrenalectomy.

5.4.5 Recurrence and death

Five (13%) of the 38 patients with CD had a relapse after 16, 25, 28, 44 and 118 months, respectively, after the first attempted curative treatment. Two of the patients with CD had died, one before TSS was performed and one who had been in remission for 7 years. None of the 17 patients with benign adrenal CS had a relapse and none had died at the end of the study. Of 21 patients diagnosed with ectopic CS, three had a relapse 34, 41 and 90 months after the first attempted curative treatment and 18 patients with ectopic CS had died at the end of the study. One of the patients with adrenal carcinoma had a relapse after 8 months and two of the three patients with adrenal carcinoma had died at the end of the study.

5.4.6 Time from debut of symptoms to remission

For patients with CD, the time from debut of symptoms to remission was 907 days (30 months) for patients who achieved remission after the first TSS and 1371 days (46 months) for patients who needed additional treatments postoperatively to achieve remission. In patients with benign adrenal CS, the total median time from debut of symptoms to remission was 723 days (24 months). The timeline is shown in Figure 7.

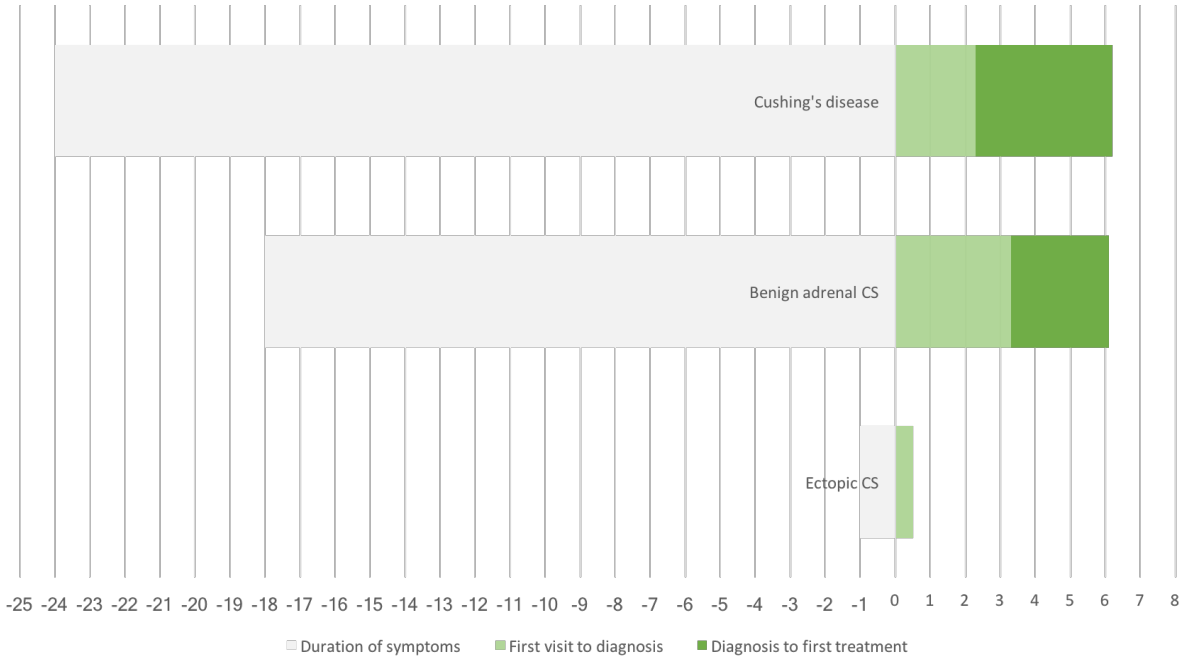

Figure 7. *Time line for patients with endogenous Cushing's syndrome (CS) in months*

6. Discussion

In this project, the epidemiology of endogenous CS in West Götaland region has been studied. The main findings of the study are: 1) Incidence rate of all endogenous CS is 3.1 per million per year and the prevalence is 57 per million. 2) Of all patients with endogenous CS, proportionally fewer patients have CD (49%) than previously reported, and more patients have benign adrenal CS (21%) and ectopic CS (26%). 3) Validation of the diagnostic codes for CD has a sensitivity of 100% and a specificity of 70%, and for ectopic CS a sensitivity of 62% and a specificity of 93%. 4) New diagnostic codes for adrenal CS should be added to the ICD-registry. 5) The total time from debut of symptoms to remission is 30-46 months for patients with CD and 24 months for patients with benign adrenal CS. 6) Time with undiagnosed CS is the longest period of the disease in patients with endogenous CS.

6.1 CS in the West Götaland region

Of 234 identified patients, 80 patients had endogenous CS. CD was found in 39 patients, representing 49% of patients with endogenous CS and 65% of ACTH-dependent CS. These results differed from previous studies where CD was reported to account for 70% of all cases of CS (1) and 80% of all ACTH-dependent CS (2). Ectopic CS was found in 21 patients, representing 26% of patients with endogenous CS and 35% of ACTH-dependent CS. In previous studies, ectopic CS was reported 12% of all cases of CS (1) and 20% of ACTH-dependent CS (2). Thus, the results of this study show a larger proportion of ectopic CS than previously reported.

The differences between CD and ectopic CS in this study, compared to previous studies, can be explained by variations in the diagnostic process and management of patients with

endogenous CS. Patients with ectopic CS usually have malignant tumours, and are consequently managed at oncology departments. Different countries and hospitals may have varying routines for these patients. In patients with ectopic CS, it is likely that some patients were never admitted to endocrinology departments and never received a CS diagnosis, explaining the lower rates of ectopic CS in previous studies. Furthermore, the course of ectopic CS is often rapid and the disease can have mortal outcome in only weeks or months, increasing the difficulty of identify these patients.

In patients with ACTH-independent CS, 17 (85%) had benign adrenal CS, thus representing 21% of all endogenous CS. Three (15%) of the patients with ACTH-independent CS had adrenal carcinoma, representing 4% of all endogenous CS. These results differed from previous reports, where proportions for adrenal adenoma and adrenal carcinoma in ACTH-independent CS were 60 and 40%, respectively (2). Similar to ACTH-dependent CS, the different rates of ACTH-independent CS can be explained by differences in the management of these patients between countries and hospitals. For example, it is possible that patients with adrenal adenoma are mainly managed in departments of surgery in some hospitals, explaining the lower rates of adrenal adenoma in previous studies.

6.2 Validation of the CS diagnosis

Aetiology of ACTH-secreting pituitary adenoma was proven through histopathological diagnosis in 77% of the patients with CD in the current study, which is in line with previously reported rates of 74% (4). Furthermore, the vast majority of patients with CD in this study who had invisible or small pituitary adenoma were investigated with sinus petrosus catheterization. Thirty-six (92%) of the 39 patients with CD had confirmed diagnosis with

histopathological examination and/or sinus petrosus catheterization. Almost all patients with ACTH-independent CS had confirmed aetiology through histopathological diagnosis, 16 (94%) of 17 patients with benign adrenal CS and all three patients with adrenal carcinoma.

All 39 patients diagnosed with CD received the right diagnostic code for pituitary dependent CS, E24.0. The sensitivity of the diagnostic code was 100% and the specificity 70%, indicating well-functioning diagnostic coding for patients with CD although the diagnostic code was apparently also used incorrectly for several patients who did not have CD.

In the patients with benign adrenal CS, 47% received the diagnostic code E24.8 (Other specified CS) and 53% received E24.9 (Unspecified CS). The fact that there is no separate diagnostic code for adrenal CS explains the inconsistent coding of these patients.

The majority (62%) of the patients with ectopic CS received the right diagnostic code (E24.3). The remaining patients received various diagnostic codes. The sensitivity of the diagnostic code was only 62%, meaning that one-third of patients with ectopic CS are not captured by a search for this specific diagnostic code. Patients with ectopic CS are often managed at oncology clinics, possibly explaining the lower sensitivity of this diagnostic code.

In the patients with adrenal carcinoma, one received E24.8 (Other specified CS) and one received E24.9 (Unspecified CS). The third patient with adrenal carcinoma had not received any diagnostic code for CS. All three patients with adrenal carcinoma received, however, the diagnostic code for adrenocortical cancer, C74.0. Again, since there is no separate diagnostic code for adrenal CS, the diagnostic coding of these patients is inconsistent. In future studies, the diagnostic code for adrenocortical cancer should be included in the search criteria.

In summary, the results from the validation of the diagnostic codes for CS demonstrates that separate diagnostic codes for benign adrenal CS and adrenal carcinoma are needed. In fact, it

is odd that rarer subgroups of CS such as Nelson's syndrome and alcohol induced CS have separate diagnostic codes in the current ICD-registry. Concerning alcohol induced CS, we suggest that this code (E24.4) should be replaced by a code for pseudo CS, since alcohol induced CS is included in pseudo CS.

6.3 Incidence and prevalence

Previous epidemiological studies on CS are often limited to CD (Table 4) and prevalence rates has, to our knowledge, only been reported in one previous study (10). In our study, the total incidence of endogenous CS was 3.1 per million per year. For CD, the incidence was 1.5 per million per year, for benign adrenal CS 0.7, adrenal carcinoma 0.1 and ectopic CS 0.8. These incidence rates are in line with previous findings. Lindholm *et al.* (4) found an incidence of 1.2-1.7 per million per year for CD, for adrenal adenoma 0.6 and for adrenal carcinoma 0.2. Arnardóttir *et al.* (13) and Clayton et al. (14) both found an incidence of 1.5 per million per year for CD and Bolland *et al.* (10) found an incidence of 1.8 per million per year for endogenous CS, excluding malignant ectopic CS and adrenal carcinoma. Furthermore, in a study on the incidence of pituitary adenomas in West Götaland region, Sweden (15) the total incidence of ACTH-secreting pituitary adenomas, *i.e.* CD, was 1.8 per million per year. Higher incidence rates, 2.4 per million per year for CD, were found by Etxabe *et al*. (16). Broder *et al.* (11) reported an exceptionally high annual incidence rate for all endogenous CS, 49 cases per million, and 8 cases per million for CD. Interestingly, that study was based on data from a large insurance database, probably greatly overestimating the incidence of CS.

Table 4. *Incidence rates of endogenous CS in epidemiological studies*

Study	Study period	Country	No. of patients	All endogenous CS	Cushing's disease	Adrenal adenoma	Ectopic CS	Adrenal carcinoma
Etxabe et al.	1975-1992	Spain	49		2.4			
Lindholm et al.	1985-1995	Denmark	166		1.2-1.7	0.6		0.2
Arnardóttir et al.	1955-2009	Iceland	19		1.5			
Clayton et al.	1958-2010	UK	60		1.5			
Bolland et al.	1960-2005	New Zeeland	253	1.8*				
Tjörnstrand et al.	2001-2011	Sweden	25		1.8			
Broder et al.	2009+2010	US	522+537	49	8			
Current study	2002-2017	Sweden	80	3.1	1.5	0.7	0.8	0.1

Data are incidence rates per million per year
*Excluding adrenal carcinoma and malignant ectopic CS

The annual incidence of endogenous CS in West Götaland Region varied, in 2003 only one patient was diagnosed with benign adrenal CS compared to in 2013 when 11 new cases of endogenous CS were reported (Figure 5). Although we cannot exclude that some patients with true CS may have been missed, this is probably a finding by chance.

The prevalence rate of endogenous CS in this study was lower, 57 cases per million, than previously reported 79 cases per million (10). It is possible that some patients who were treated before 2002, who are considered cured and therefore no longer are followed at the endocrinology department at the Sahlgrenska University Hospital, may have been missed. Hence, the true prevalence rate of endogenous CS in the West Götaland region may be somewhat higher.

6.4 Demographics

In our study, women accounted for 70% of all endogenous CS, which is in line with previous reports (10). The mean age at diagnosis was 50 years. In previous studies, the mean age at diagnosis has been reported to be 25-50 years (1) and median age at diagnosis 36-46 years (14). Thus, our study showed a somewhat higher mean age at diagnosis than previously

reported, possibly explained by the higher proportion of patients with ectopic CS in our study. In fact, patients with ectopic CS (mean age 59 years) were significantly older at diagnosis compared to patients with CD (mean age 48 years) and benign adrenal CS (mean age 44 years).

At the time of diagnosis, 74% of the patients had hypertension and 33% had diabetes. In a previous study, the prevalence of hypertension was reported 68% and diabetes or glucose intolerance 80% (1). Our study found a somewhat higher prevalence of hypertension and for diabetes, a considerably lower prevalence than previously reported. The differences can be explained by variations in diagnostic criteria for hypertension, and the much higher prevalence of diabetes in the previous study by the fact that patients with glucose intolerance were also included.

6.5 Timeline

To our knowledge, a timeline from debut of symptoms to recognition, diagnosis, treatments and remission for patients with endogenous CS has not previously been created.

Bolland *et al.* (10) reported a duration of symptoms of 2 years for CS (excluding adrenal carcinoma and malignant ectopic CS) which is in line with our results with duration of symptoms of 24 months for CD and 18 months for benign adrenal CS. Differences in time from first visit to the first attempted curative treatment in patients with CD compared to benign adrenal CS did not differ significantly. This may be a surprising finding since the biochemical testing for CD is often more time consuming compared to benign adrenal CS. In patients with adrenal adenoma, low ACTH and CT adrenal are most often sufficient to confirm the diagnosis and refer the patient for adrenalectomy. For patients with CD, sinus

petrosus catheterization is frequently needed, making the diagnostic process longer. When comparing the time from debut of symptoms to first treatment between women and men with CD and benign adrenal CS, the time did not differ significantly. However, patients with ectopic CS had significantly shorter duration of symptoms and time from first visit to diagnosis than both CD and benign adrenal CS.

Of 38 patients with CD, 35 (92%) were in remission at last visit. Of these 35 patients, 25 (69%) achieved remission after the first TSS, one (2%) after pituitary radiotherapy and 10 (29%) required additional treatments to achieve remission. Previous studies have reported 82-86% remission rates after the first TSS (17) (18) and long-term remission rates of 56% (19). Thus, the remission rates of CD in our study, especially remission at last visit, are satisfying. In patients with benign adrenal CS, all 17 patients were in remission at last visit and achieved remission shortly after unilateral or bilateral adrenalectomy. Only three (14%) of the patients with ectopic CS achieved remission and none of the patients with adrenal carcinoma achieved remission.

Five patients with CD (13%) had a relapse and two patients (5%) had died. The relapse rate is in line with previous studies where 9% of the patients with CD had recurrent disease (18). None of the patients with benign adrenal CS had a relapse or had died. In contrast, 18 patients with ectopic CS and two of the three patients with adrenal carcinoma had died at the end of the study. These results confirm the much poorer prognosis of ectopic CS compared to CD and cortisol producing adrenal adenoma (10).

6.6 Strengths and weaknesses

Our search for patients was facilitated through the DRG-registry and the collected data was reviewed by an endocrinologist at the Sahlgrenska University Hospital who had personally been involved in the diagnostic work-up and treatment decisions in most of the patients included in the study. Also, since all patients with endogenous CS in the West Götaland region should be referred to the endocrinology department of the Sahlgrenska University Hospital, we feel confident that all patients diagnosed with CS from 2002 to 2017 in the West Götaland region were included in the study after searching the DRG-registry.

However, we cannot completely rule out that some patients with endogenous CS in the West Götaland region who have not received any diagnostic code for CS at the Sahlgrenska University Hospital may have been missed. For example, it is possible that some patients with ectopic CS who were diagnosed and treated in local hospitals in the region and were never admitted to the Sahlgrenska University Hospital were missed. Thus, it is likely that the true incidence and prevalence rates for endogenous CS, especially for ectopic CS, are somewhat higher. In future studies, the DRG-registry should be searched in all local hospitals in the West Götaland region for the diagnostic codes of CS, and also include the diagnostic codes for adrenal cancer (C24.0), benign pituitary tumour (D35.2) and malign pituitary tumour (C75.1), to make sure that all patients with endogenous CS are identified.

A strength of this study is the analysis of the incidence and prevalence in all subgroups of endogenous CS, which has not previously been done. The methods used for calculation of incidence and prevalence rates are generally accepted and the West Götaland region has a large and well-defined population. Since the calculations are based on reliable data, the incidence and prevalence rates should be considered accurate. However, calculations were

made on a relatively small study population (N=80), and subgroups of CD, benign adrenal CS, ectopic CS and adrenal carcinoma are even smaller, decreasing the power of the study.

Validation of the ICD-10 codes for CS has not been reported previously. Weaknesses of the current ICD-registry were identified, especially the lack of diagnostic codes for adrenal CS. Calculations of sensitivity and specificity for the diagnostic codes E24.0 (Pituitary-dependent CS), E24.2 (Iatrogenic CS) and E24.3 (Ectopic CS) gives an approximate estimate of the reliability of the diagnostic coding for these diagnoses. However, since the sensitivity and specificity for benign adrenal CS and adrenal carcinoma were not estimated due to inconsistent coding, it is not possible to draw conclusions on the reliability of the diagnostic coding for all endogenous CS.

The novel timeline analysis illustrates the time lapse from debut of symptoms through recognition, diagnosis and treatment to remission, and can be used to evaluate and improve the patient care in patients with endogenous CS. However, the timeline has several limitations. The dates of all patient visits were not always accessible and in some cases dates were roughly estimated. Thus, time differences may not be entirely accurate and would probably differ if they were re-calculated. Duration of symptoms was usually based on the patients' own description on debut of characteristic symptoms of CS. Duration of symptoms is a highly subjective estimate that depends not only on the patient's own experience of the symptoms but also on the treating physician's assessment and the person that reviews the data. Furthermore, remission status and relapse were difficult to determine in some patients and estimates may not be entirely correct.

7. Conclusions and implications

This study provides reliable incidence and prevalence rates for endogenous CS, with an overall incidence rate of 3.1 per million per year and a prevalence of 57 per million. CD was less common than previously reported (2), representing 49% of all patients with endogenous CS, while benign adrenal CS counted for 21% and ectopic CS for 26% of the patients, which are considerably higher numbers than previously reported (2). Although incidence and prevalence rates in our study were generally in line with previous reports, the study population and the subgroups are small. Further research, preferably on larger populations in different geographical areas, is necessary to establish the true incidence and prevalence rates of CS.

Validation of the diagnostic codes used for CS was performed and suggestions on how to improve the diagnostic coding of CS are presented. Most importantly, new diagnostic codes for benign adrenal CS and adrenal carcinoma should be added to the ICD-registry. Our validation of the diagnostic codes for CS open up to further evaluation of the diagnostic coding not only for CS but for other diseases as well. Validation of the diagnosis is of paramount importance in epidemiological research of rare diseases for identification of patients. Additionally, adequate follow-up of these patients is facilitated through accurate diagnostic coding. Hence, diagnostic coding should also be considered an important matter in patient care.

A timeline demonstrates the time span from debut of symptoms to remission. For patients with CD, the total time from debut of symptoms to remission is 30-46 months and in patients with benign adrenal CS 24 months. The timeline can preferably be further developed in future studies and should also be investigated in other hospitals for comparison. Our findings show

that time with undiagnosed CS prior to referral to an endocrinologist is the longest period of the disease. Because duration of hypercortisolism before CS diagnosis may predict increased mortality (9) and most patients with endogenous CS actually achieve remission with adequate treatment, physicians need to have CS in mind and not miss these rare patients that easily can be overlooked among the big group of patients with the metabolic syndrome. Since diabetes and in particular hypertension is frequent in patients with active CS, it is possible that screening for CS in these patient groups should be done more often.

CS is associated with increased morbidity and mortality (10) and patients in long-term remission maintain a high cardiovascular risk (7), suggesting the importance of early recognition and adequate management of these patients. Our timeline can be used to further evaluate and improve the time lapse of the patient care in patients with endogenous CS at the Sahlgrenska University Hospital. Endocrinologists at the Sahlgrenska University hospital have established a structured short- and longterm management plan for CS patients in remission (20) where evaluation of cardiovascular risk, pituitary function as well as psychiatric symptoms are emphasized. The aspect of psychiatric dysfunction in patients with CS in remission is not yet fully understood and is subject for future research.

Populärvetenskaplig sammanfattning

Cushing's syndrom i västra Sverige

Examensarbete, Läkarprogrammet

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Cushing's syndrom (CS) är en ovanlig hormonsjukdom som beror på för höga nivåer av stresshormonet kortisol i kroppen. Kortisol är ett livsnödvändigt hormon som påverkar många av kroppens funktioner, bland annat sömnen, ämnesomsättningen och hjärnan. Kortisol tillverkas normalt av binjurarna, vars produktion i sin tur styrs från en liten körtel i hjärnan, hypofysen. Hypofysen tillverkar adrenokortikotropt hormon (ACTH), vilket stimulerar binjurarna att tillverka kortison. Hos en frisk människa reglerar kroppen själv så att nivåerna av kortisol i kroppen är lagom höga.

Hos personer med CS är nivåerna av kortisol mycket höga, vilket är skadligt för kroppen. Personer med CS går upp i vikt, får högt blodtryck och upplever psykiska besvär. Orsaken till sjukdomen är oftast en tumör som tillverkar hormon. Antingen tillverkar tumören kortisol (binjuretumörer) eller ACTH (hypofystumörer), vilket gör att nivåerna av kortisol i kroppen höjs. Tumörerna är oftast godartade, även om CS i ovanligare fall kan orsakas av cancertumörer.

Den vanligaste behandlingen för CS är att man opererar bort den hormontillverkande tumören. Oftast blir personen då botad. Forskning har dock visat att hjärt-kärlsjukdom är

vanligare hos personer med CS, även efter att de har blivit botade. Eftersom CS är en ovanlig sjukdom, finns inte mycket forskning inom området.

I denna studie har incidens (hur många personer som insjuknar i sjukdomen per år per miljon invånare) beräknats för CS i Västra Götaland. Man har också undersökt hur välfungerande de olika diagnoskoderna för CS är, vilka används för att registrera sjukdomen i journalen. Dessutom har en tidslinje gjorts från att personerna med CS började känna sig sjuka tills första läkarbesöket, behandling och bot. 80 personer med CS som fått diagnosen i Västra Götaland mellan åren 2002-2017 ingår i studien.

I studien kom man fram till att incidensen av alla typer av CS är 3 per miljon per år i Västra Götaland. Av personerna med CS hade 49% godartad hypofystumör, 21% godartad binjuretumör, 4% binjurecancer och 26% hormonproducerande cancertumör i någon annan del av kroppen. För personer med godartad hypofystumör tog det 30–46 månader från de började få symtom från sjukdomen tills de ansågs botade. För personer med godartad binjuretumör tog det 24 månader. Endast 14% av personerna med hormonproducerande cancertumörer och inga av personerna med binjurecancer botades.

Denna studie visar nya siffror på incidens av CS som bekräftar hur ovanlig sjukdomen är. Andelen personer med hormonproducerande cancertumörer var större i denna studien jämfört med tidigare studier och mer forskning behövs för att säkerställa om detta stämmer. Diagnoskoderna som användes för CS visade sig vara i behov av uppdatering med nya diagnoskoder för binjuretumörer eftersom inga separata diagnoskoder fanns för det. Tidslinjen som gjordes kan användas som ett verktyg för att förbättra vården av personer med CS, så att sjukdomen upptäcks tidigt, rätt behandling ges och de blir botade snabbare.

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