Cushing’s syndrome in children and adolescents: a Danish nationwide population-based cohort study

Johanne Marie Holst¹, Erzsébet Horváth-Puhó², Rikke Beck Jensen³, Mariane Rix⁴, Kurt Kristensen³, Niels Thomas Hertel⁵, Olaf M Dekkers², Henrik Toft Sørensen², Anders Juul³ and Jens Otto L Jørgensen¹

Departments of ¹Internal Medicine and Endocrinology and ²Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark, ³Department of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, ⁴Department of Pediatrics, Aalborg University Hospital, Aalborg, Denmark, ⁵Department of Pediatrics, Aarhus University Hospital, Aarhus, Denmark, and ⁶Hans Christian Andersen Children’s Hospital, Odense University Hospital, Odense, Denmark

Abstract

Objective: Cushing’s syndrome (CS) affects all age groups, but epidemiologic data in young patients are very limited. We therefore examined the incidence, prevalence and hospital morbidity of CS in children and adolescents.

Design: In a nationwide cohort study, we included all Danish citizens aged 0–20 years from 1977 to 2012. Data were obtained from the Danish National Patient Registry using the International Classification of Diseases (ICD) codes and the Danish Civil Registration System. The diagnosis and treatment were validated by means of individual patient charts. Incidence rate of CS patients aged 0–20 years at diagnosis were computed (standardized to the age and sex distribution of the Danish population). The patients were followed for a maximum of 36 years. Standardized incidence ratios (SIRs) of different hospital-recorded outcomes based on the ICD codes in patients with CS compared to the general population were assessed.

Results: We identified a total of 40 pediatric patients with CS, yielding an annual incidence of 0.89 cases/10⁶ population (95% confidence interval (CI) = 0.63–1.16). The median age at the time of diagnosis was 13.8 years (interquartile range: 10.5–18.2 years), 58% were female and 70% had adrenocorticotropic hormone-producing pituitary adenomas. During follow-up, CS patients (excluding three malignant cases) were at increased risk of being diagnosed with infections (SIR: 3.24, 95% CI: 1.05–7.54) and infertility (SIR: 4.56, 95% CI: 1.48–10.63). The three patients with an adrenocortical carcinoma died shortly after diagnosis, but mortality was not increased in the remaining patients.

Conclusions: CS is rare in the pediatric population. The risk of morbidity related to infections and infertility is elevated and merits further attention.

Introduction

Cushing’s syndrome (CS), caused by prolonged exposure to excess glucocorticoids, is a serious condition associated with excess morbidity and mortality (1, 2). Endogenous causes include adrenocorticotropic hormone (ACTH)-dependent forms resulting from either an ACTH-secreting pituitary adenoma (i.e. Cushing’s disease (CD)) or an ectopic ACTH-secreting tumor. ACTH-independent forms include unilateral benign and malignant cortisol-producing adrenal tumors, as well as bilateral adrenal lesions. In contrast to iatrogenic CS, which is common, endogenous CS is a rare condition with a reported annual incidence of ≈2.0–2.5/10⁶ population in Denmark (1).
CD accounts for 60% and benign adrenal adenomas for 25% of endogenous CS (1). The mean age at diagnosis is 44 years and 75% of cases are women (2).

CS in children and adolescents is estimated to comprise 10% of diagnosed cases, but population-based epidemiological data are lacking (3). As in adults, CD remains the most common cause of endogenous CS in children (85%), with a female predominance (4) (although a male predominance has been reported in prepubertal children (5, 6, 7). The onset of the disease is insidious, but its hallmark is obesity combined with longitudinal growth retardation (4, 5). The primary treatment of CS is surgery, and the success rate in terms of remission of hypercortisolism appears to be high in both children and adults (5). Despite surgical control, CS in children is associated with somatic and psychosocial complications (4) that warrant early diagnosis and meticulous follow-up.

We therefore conducted a nationwide cohort study to examine the incidence and prevalence of CS in children and adolescents and the risk of subsequent hospital-recorded selected morbidity compared with the general population.

Subjects and methods

Source population

The source population consisted of the age group of 0–20 years in Denmark between 1977 and 2012. Data were obtained from the Danish Civil Registration System (CRS) (8) and the Danish National Patient Registry (DNPR) (9). The CRS has kept electronic records on gender, age, birth date, residence, emigration date and vital status since 1968. The DNPR has recorded all hospital discharge diagnoses and surgical procedures since 1977 and all hospital outpatient specialty clinic and emergency room visits since 1995. The central personal registry number assigned to each Danish citizen at birth and to residents upon immigration allows accurate linkage of all Danish registries at the individual level. The Danish National Health Service provides universal tax-supported health care, guaranteeing free access to general practitioners and hospitals (10).

Study population

All individuals aged 0–20 years at the time of a CS diagnosis during the study period (1977–2012) were identified from the DNPR. The cumulative population size of 0- to 20-year-old individuals in the study period was 4,678,038 persons. Patients diagnosed with adrenocortical carcinoma (ACC) were included in the incidence data but not in the analysis of outcomes. The International Classification of Diseases, Eighth Revision (ICD-8) and Tenth Revision (ICD-10) codes used in the study are provided in the Supplementary Appendix (see section on supplementary data given at the end of this article) (ICD-9 has never been used in Denmark). Throughout the paper, the term CS is used to describe the cohort of patients with Cushing’s syndrome except for the patients with ACC (unless otherwise specified).

The CS diagnosis is based on a combination of clinical characteristics, each of which are not pathognomonic, and biochemical tests that are not infallible and prone to diagnostic misclassification (11). To minimize misclassification, we added surgical intervention within three years after a CS diagnosis as an additional eligibility requirement (12).

Hospital records were subsequently retrieved, and the authors performed a review of all patients’ individual medical records. A diagnosis of CS was made when laboratory testing, imaging and treatment were in agreement. Uncertainties were discussed among the authors until consensus was reached.

Follow-up

Follow-up started on the date of initial CS diagnosis. Follow-up was censored when an outcome of interest occurred, when death or emigration took place, or on 31 December 2012, whichever came first. The patients were thus followed for a maximum of 36 years (maximum age at the end of follow-up was 54.5 years).

Study outcomes

We computed the first hospital-recorded occurrence of infection, infertility, fracture or osteoporosis, cancer, epilepsy, diabetes, venous thromboembolism (VTE), acute myocardial infarction (AMI), stroke and heart failure after the CS diagnosis. Inpatient and outpatient diagnoses registered in the DNPR were used to identify these outcomes. Each hospital discharge or outpatient visit is recorded in the DNPR with one primary diagnosis and one or more secondary diagnoses classified according to ICD-8 until the end of 1993 and ICD-10 thereafter. Where possible, we examined available individual patient records to confirm the outcomes.
Statistical analysis


We computed the standardized incidence rate of CS in children and adolescents (standardized to the age and sex distribution of the Danish population ≤20 years in the year 2000). The standardized incidence rate was calculated for the overall 1977–2012 study period. The point prevalence per 10^6 population was calculated on 1 January 2012 by dividing the number of prevalent CS cases by total number of Danish children and adolescents on the given date.

We then used the cumulative incidence (risk) function, accounting for death as a competing risk, to calculate the risk of outcomes based on ICD codes (infection, infertility, fracture or osteoporosis, cancer, epilepsy, diabetes, VTE, AMI, stroke and heart failure) during the follow-up period. To compare the incidence of different outcomes in individuals with a diagnosis of CS with that of the general population, we computed standardized incidence ratios (SIRs), i.e. the ratio of the observed to the expected number of CS. The expected number of cases with outcome was calculated by multiplying national incidence rates of groups defined by age (five-year intervals), sex and five-year calendar intervals by the corresponding person-years at risk in the CS cohort. For estimation of 95% confidence intervals (CIs), we assumed that the number of outcomes followed a Poisson distribution. Exact 95% CIs were used since the observed numbers were less than ten. Patients with an outcome diagnosis prior to or at the time of CS diagnosis were excluded from the calculation of SIR. All analyses were repeated after classifying CS patients according to their ACTH dependency status. The information about hypopituitarism, permanent hydrocortisone replacement and the duration between first hospital admission and last surgery was retrieved from the patient records. Analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC, USA).

The study has been approved by the Danish Health and Medicines Authority (record no. 3-3013-423/1/) and by the Danish Data Protection Agency (record no. 11-88-37-29).

Results

Study population

A total of 256 patients diagnosed with CS were identified initially from the DNPR. Of these, 33 patients had a surgical intervention code. According to medical record review, three of these 33 patients did not have CS. Of the 223 cases with a CS diagnosis code and no surgical intervention code in the DNPR, medical record review revealed ten patients who indeed had undergone a surgical intervention to treat CS (Fig. 1A). One patient diagnosed with CS, who underwent a surgical intervention shortly after end of the follow-up period, was included in the analysis.

Patient characteristics

In total, we identified 40 patients with CS meeting our inclusion criteria (Fig. 1B). Twenty-nine patients had ACTH-dependent CS (72.5%), including one patient with ectopic disease (ACTH-secreting nephroblastoma). Eleven patients had ACTH-independent CS (27.5%) of whom four had a unilateral adenoma (10.0%), four had bilateral hyperplasia (10.0%) and three had ACC (7.5%). Three patients with CD had multiple endocrine neoplasia type 1 (MEN-1). One patient with CD also was diagnosed with Klinefelter syndrome, and one patient with bilateral...
adrenal disease was diagnosed with primary pigmented nodular adrenocortical disease (PPNAD) as a component of the Carney complex. One patient with unilateral adrenal disease was diagnosed with craniofrontonasal syndrome. Prior to the CS diagnosis, one patient was diagnosed with anorexia nervosa. The three patients diagnosed with ACC (all females, median age at diagnosis: 18.4 years) were included in the estimation of the standardized incidence rate but excluded from other analyses. Demographic data on the CS patients at the time of diagnosis are provided in Table 1. The median age of CS patients at diagnosis was 12.9 years (interquartile range: 10.5–17.8 years) and 54% were female. In the ACTH-independent group, 88% were female (not including the three patients with ACC).

Incidence, prevalence and mortality

The standardized incidence rate of CS in children and adolescents are shown in Figure 2.

The annual incidence of pediatric CS in the overall study period (1977–2012) was 0.89 cases/10^6 population (95% CI = 0.63–1.16). The point prevalence in 2012 was 26 cases/10^6 population (95% CI = 18.9–35.8). The three CS patients who died during follow-up all had ACC.

Symptoms prior to diagnosis

Symptoms and signs prior to the CS diagnosis date were identified by medical record review of all patients with confirmed CS. Among those, 80% were obese and 53% had impaired linear growth. Additional symptoms and signs of CS included moon face and facial plethora (82.5%), truncal obesity (70%), buffalo hump (37.5%), hypertension (37.5%), striae (25%), myopathy (17.5%), easy bruising (17.5%), fatigue (15%), acne (15%), hirsutism (15%), psychiatric symptoms (15%) and headache (7.5%).

Seven out of eight female patients aged ≥12 years at the time of diagnosis had oligomenorrhea (the median age at the time of CS diagnosis of these seven patients was 19.7 (interquartile range: 16.3–20.1)).

Treatment

Twenty-four of the 28 patients with CD underwent transsphenoidal surgery (TSS) as first-line treatment, of which two were preoperatively treated with metyrapone and pasireotide for a short period. Six of the 24 patients undergoing TSS had a second pituitary operation, whereas one underwent bilateral adrenalectomy as second-line treatment. One of the 24 patients underwent bilateral adrenalectomy after a transsphenoidal re-operation; this patient also had a third transsphenoidal operation, stereotactic pituitary radiation therapy as subsequent treatment for Nelson’s syndrome and was briefly treated with ketoconazole. Of the remaining four patients with CD, two underwent radiation as first-line treatment followed by TSS, which in one of the patients was preceded by short-term treatment with metyrapone and aminoglutethimide, one received stereotactic pituitary radiation therapy as monotherapy and one underwent bilateral adrenalectomy followed by TSS for Nelson’s syndrome. The patient with ectopic disease underwent nephrectomy, irradiation and chemotherapy. The eight patients with unilateral adrenal adenoma and bilateral hyperplasia underwent unilateral and bilateral adrenalectomy respectively. The three patients with ACC

Table 1  Baseline characteristics at the time of diagnosis in the Cushing’s syndrome cohort.

<table>
<thead>
<tr>
<th>Cushing cohort (n = 37)</th>
<th>n</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–14</td>
<td>21</td>
<td>56.8</td>
</tr>
<tr>
<td>15–20</td>
<td>16</td>
<td>43.2</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>54.1</td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td>45.9</td>
</tr>
<tr>
<td><strong>Year of Cushing’s syndrome diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1977–1990</td>
<td>14</td>
<td>37.8</td>
</tr>
<tr>
<td>1991–2000</td>
<td>13</td>
<td>35.1</td>
</tr>
<tr>
<td>2001–2012</td>
<td>10</td>
<td>27.0</td>
</tr>
</tbody>
</table>

Figure 2

Standardized incidence rate per 10^6 person-years according to year (1977–2012).

Downloaded from Bioscientifica.com at 08/08/2019 08:25:56PM via free access
all had surgery as part of their treatment. The median duration between the first hospital admission and the last surgery in all 40 patients was 5.0 months (interquartile range, 2.0–18.0 months).

Study outcomes

The cumulative incidence curves of the hospital-recorded outcomes (fracture and osteoporosis, infection, cancer, epilepsy and infertility) are shown in Figure 3.

CS patients were at increased risk of being diagnosed with infertility (SIR: 4.56, 95% CI: 1.48–10.63) (Table 2). The median age of receiving an infertility diagnosis was 27.0 years, and four of the five patients were women. Three patients had ACTH-dependent disease and were treated with either TSS or stereotactic pituitary radiation. Neither the patient with Klinefelter nor the patient with anorexia nervosa received a diagnosis of infertility.

CS patients were at increased risk of being diagnosed with infections (SIR: 3.24, 95% CI: 1.05–7.54) (Table 2), and when classified according to ACTH dependency, the risk of infection was more pronounced in the ACTH-independent group (infections: SIR: 5.72, 95% CI: 1.18–16.71 vs SIR: 1.96, 95% CI: 0.24–7.07). The risk of infection appeared to be higher among patients receiving hydrocortisone replacement. Thus, 28.6% (n=4) of patients on hydrocortisone replacement (n=14) were subsequently diagnosed with an infection, whereas only 4.3% (n=1) of patients not receiving hydrocortisone (n=23) had this diagnosis. None of the patients were diagnosed with infection more than twice. Four patients, of whom two were on hydrocortisone replacement, received a diagnosis indicative of acute adrenocortical failure, which in one case concurred with a diagnosis of infection.

Three patients were diagnosed with fractures or osteoporosis (SIR: 1.76, 95% CI: 0.36–5.15). Two patients were diagnosed with cancer (renal cell carcinoma and cervical adenocarcinoma in situ respectively) (SIR: 2.74, 95% CI: 0.33–9.90). Epilepsy was diagnosed in one patient (SIR: 2.98, 95% CI: 0.08–16.62), and no patients were diagnosed with diabetes, VTE, AMI, stroke or heart failure (data not shown).

Seventeen patients developed hypopituitarism as a consequence of either TSS or stereotactic pituitary radiation. Fourteen patients received permanent hydrocortisone replacement post-treatment, of which ten had ACTH-dependent disease.

Table 2 Standardized incidence ratios for the risk of infection, fracture and osteoporosis, epilepsy, infertility and cancer in patients with Cushing’s syndrome.

<table>
<thead>
<tr>
<th>Person-years at risk</th>
<th>Observed No.</th>
<th>Expected No.</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>590.15</td>
<td>5</td>
<td>1.55</td>
</tr>
<tr>
<td>Fracture and osteoporosis</td>
<td>555.50</td>
<td>3</td>
<td>1.70</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>641.43</td>
<td>1</td>
<td>0.34</td>
</tr>
<tr>
<td>Infertility</td>
<td>618.66</td>
<td>5</td>
<td>1.10</td>
</tr>
<tr>
<td>Cancer</td>
<td>666.71</td>
<td>2</td>
<td>0.73</td>
</tr>
</tbody>
</table>

CI, confidence interval; NA, not applicable; No, number; SIR, standardized incidence ratio.

Discussion

In this nationwide population-based cohort study, we confirmed that CS is a rare disease with an annual incidence of 0.89 cases/106 population of CS in children and adolescents. We observed an increased risk of hospital-recorded infections and a hospital clinic code of infertility during long-term follow-up.

The strengths of our study include the population-based design and linkage among health-related registries. The study, however, also has limitations that merit attention. All patients with CS in Denmark between 1977 and 2012 were identified, but the absolute number of patients and outcomes was very low and the study had a maximum of 36 years of follow-up. Moreover, we did not include data on neuropsychiatric and cognitive complications, which have been reported to be frequent...
even among patients with biochemically controlled disease (4).

Data from the DNPR are used routinely in nationwide quality monitoring of treatment (13, 14). However, data quality varies by ICD diagnosis (15). The majority of misclassified patients in our study were referred for suspected CS, and the diagnosis was eventually discarded. To reduce misclassification, we included an additional eligibility criterion in terms of a pertinent surgical intervention diagnosis (adrenalectomy or pituitary surgery). The patients treated with nephrectomy and stereotactic radiation therapies were not captured by this eligibility criterion, and surgical interventions were incorrectly recorded in nearly a quarter of patients diagnosed with CS. It is noteworthy that outpatient ICD diagnoses were not included until 1995, which may have influenced the outcome diagnoses. However, the CS diagnosis and treatment of each individual patient ultimately included in our study were validated via patient charts, so we feel confident that the figures regarding incidence and differential diagnosis are accurate.

The annual incidence of CS in this study is low as compared to those reported in populations including both children and adults (1, 16). In accordance with earlier studies (1, 5, 12, 16), we observed a predominance of females. The gender distribution of our pediatric patients was more even than that in adult CS patients. A male-to-female predominance among pediatric patients in general has previously been described in one study (17), and a male-to-female predominance among subgroups of pediatric patients has also been reported (5, 6, 7).

Our study showed that pediatric CS patients were at increased risk of being diagnosed with infections in a hospital after the diagnosis, in line with adult data (12, 18), but increased infection risk was not reported in a recent review of long-term outcomes in children treated for CS (4). The true incidence of infections in our cohort could be underestimated, as only hospital visits are reported to the DNPR. On the other hand, patients with CS are followed as outpatients on a regular basis, which may lead to increased diagnostic awareness and the risk of detection bias. It is also noteworthy that a diagnosis of infection was more frequent among patients receiving hydrocortisone replacement, which could suggest that relative adrenocortical failure could have been an underlying or contributing cause of the hospitalization and subsequent diagnosis.

Menstrual irregularity and fertility problems are common in women with CS, most likely prompted by hypercortisolemia (19). Infertility became an ICD-10 diagnosis only in 1994, and due to left truncation, some CS patients in our cohort may have had undiagnosed or non-recorded infertility, but our study did not measure infertility based on strict epidemiological measures. Still, we found an increased risk of diagnosed infertility after treatment among adolescent CS patients. This observation merits further investigation and attention from treating physicians.

Previous studies have showed that hypercortisolemia in children may also increase the long-term risk of osteoporosis (20), and our study also suggest an increased risk of osteoporosis and fractures.

Recent meta-analyses report that adult CD is associated with increased mortality (21), even among patients in biochemical remission (22). This increased mortality risk was not documented in the present CS population, but this may be due to inadequate statistical power and insufficient length of follow-up period. The risk of being diagnosed with cancer is increased in adult patients with CS (12), whereas cancer as an outcome to our knowledge has not previously been examined in pediatric patients. Our data suggest that this group also is at an increased risk of being diagnosed with cancer; however, the absolute number was very low (n = 2).

The medical history of some of our patients merits consideration. As previously published, one patient was diagnosed with PPNAD as part of the Carney complex (23), a disorder characterized by an increased risk of certain tumors due to mutations in the PRKAR1A gene (24). This observation accords with previous data on CS in children and adolescents (25). MEN-1 is a genetic disorder associated with neoplastic lesions in the pituitary gland, the parathyroid glands and the endocrine pancreas (26). Three patients with CD in our cohort had MEN-1, which has previously been described (27). One patient with CD also had Klinefelter syndrome, a sporadic genetic disorder in males characterized by two or more X chromosomes, with a prevalence of 1–2 cases/1000 males. The hallmark is hypogonadism and infertility. Apart from one instance of an ectopic ACTH-producing tumor in a patient with Klinefelter syndrome, no associations between the two syndromes have been reported previously (28). Craniofrontonasal syndrome is an X-linked malformation syndrome caused by mutations in the ephrin-B1 gene (29). One patient with adrenal CS suffered from this rare disease, which to our knowledge, has not been reported previously. Prior to the CS diagnosis, one patient was diagnosed with anorexia nervosa, which may have developed in response to glucocorticoid-induced weight gain. It is therefore important to be aware that
an underlying disease such as CS may occasionally masquerade as an eating disorder (30, 31).

In conclusion, this population-based cohort study provided new population-based estimates of the incidence and prevalence rates of CS in children and adolescents. An elevated risk of certain conditions attributable to complications of the syndrome was reported.

Supplementary data
This is linked to the online version of the paper at [http://dx.doi.org/10.1530/EJE-16-0843](http://dx.doi.org/10.1530/EJE-16-0843).

Declaration of interest
Dr Sørensen did not report receiving fees, honoraria, grants or consultancies. Department of Clinical Epidemiology is, however, involved in studies with funding from various companies as research grants to (and administered by) Aarhus University. None of these studies have relation to the present study. All other authors have nothing to declare.

Funding
This study was supported by a grant from the Clinical Epidemiological Research Foundation in Denmark and the Program for Clinical Research Infrastructure (PROCIRIN) established by the Lundbeck Foundation and the Novo Nordisk Foundation.

Author contribution statement
Johanne Marie Holst, Erzsébet Horváth-Puhó, Rikke Beck Jensen, Mariane Rix, Kurt Kristensen, Niels Thomas Hertel, Olaf M Dekkers, Henrik Toft Sørensen, Anders Juul and Jens Otto L Jørgensen (DMSc) made substantial contributions to the study design and the acquisition and interpretation of the data. Erzsébet Horváth-Puhó and Johanne Marie Holst completed all analyses. Johanne Marie Holst and Jens Otto L Jørgensen drafted the manuscript. All authors contributed to the revision and completion of the article and provided their final approval of the version to be published. Johanne Marie Holst and Erzsébet Horváth-Puhó had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References
9 Schmidt M, Schmidt SAJ, Lynge Sandegaard J, Ehrenstein V, Pedersen L & Toft Sørensen H. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clinical Epidemiology* 2015 7 1–42. (doi:10.1247/CLEP.991125)

www.eje-online.org