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CLINICAL STUDY

Increased use of antimicrobial agents and hospital admission for infections in patients with primary adrenal insufficiency: a cohort study

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Abstract

Background: Previous studies have suggested that infections are an important cause of death in patients with Addison's disease, but epidemiological studies on the frequency of infections in this population are lacking.

Objective: To assess and compare the incidence risk of infections in patients with primary adrenal insufficiency with controls.

Design and setting: We conducted a cohort study, using data from the Dutch PHARMO record linkage system, that links patients' demographics and medication histories to hospital admissions.

Patients: From a cohort of oral glucocorticoid users, 390 patients with primary adrenal insufficiency were identified by assessing concurrent use of glucocorticoids and mineralocorticoids using pharmacy dispensing records. A reference cohort ($n=1933$) with the same age and sex distribution was sampled from patients not using glucocorticoids.

Outcome measure: Incidence rates and incidence rate ratios (IRR) were calculated of infections, defined by use of antimicrobial agents, as well as hospital admissions for infection.

Results: The incidence of infectious episodes, defined by usage of antimicrobial agents, among patients with primary adrenal insufficiency (incidence rate 59.2/100 person-years) was 1.5 times higher compared with controls, yielding a crude IRR of 1.61 (95% CI 1.51–1.72). The IRR decreased slightly to 1.58 (95% CI 1.47–1.70) after adjustment for co-medication and co-morbidity also associated with infection risk. Also with respect to hospital admissions for infection, the incidence rates observed for patients with primary adrenal insufficiency was higher compared with controls (3.8/100 vs 0.8/100 person-years): crude IRR 5.02 (3.66–6.87) and adjusted IRR 4.34 (95% CI 3.04–6.22).

Conclusion: Patients with primary adrenal insufficiency had an increased use of antimicrobial agents and hospital admissions related to infection.

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Introduction

Addison's disease is an autoimmune disease, leading to destruction of the adrenals and subsequent adrenal insufficiency. Its prevalence is relatively low with a reported prevalence of 93–140 per million (1). Since the introduction of glucocorticoids in 1948 life expectancy of patients with Addison's disease has increased considerably. However, even in recent studies, an increased risk of premature death in patients with Addison's disease is reported, attributed to cardiovascular diseases, neoplasms, and infections (2).

Erichsen reported infections as cause of death in 10% of Addison patients, compared with 6% in the general population (3). In addition, Bergthorsdottir found a five times higher mortality rate resulting from infectious disease in patients with Addison's disease compared with an age-adjusted background population (4). While this higher mortality could be explained by the concurrent occurrence of a life-threatening Addison crisis in these patients, it is also possible that patients with Addison's disease suffer from a higher frequency of infections or have more severe infections compared with controls.

To our knowledge, data on the incidence or severity of infectious disease in patients with Addison's disease are currently lacking. This information could be important in the treatment and follow-up of patients with Addison's disease, in order to reduce morbidity and mortality due to infections. Therefore, the objective of this study was to assess and compare the incidence of infections among patients with primary adrenal insufficiency with controls.

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Materials and methods

Setting

Data were obtained from the PHARMO record linkage system (Pharmo Institute, Utrecht, The Netherlands; available at: http://www.pharmo.nl). The PHARMO RLS includes the demographic details and complete medication history of more than two million community-dwelling residents of more than 25 population-defined areas in The Netherlands from 1985 onward, further linked to hospital admission records as well as several other health registries, including pathology, clinical laboratory findings, and general practitioner data (5). As virtually all patients in The Netherlands are registered with a single community pharmacy, independent of prescribers, pharmacy records are virtually complete with regard to prescription drugs. For this study, drug dispensing data and hospitalization data (discharge records, ICD-9) were used. Laboratory data were not available for this study. The computerized drug dispensing histories contain information concerning the dispensed drug, dispensing date, the prescriber, amount dispensed, prescribed dosage regimen, and the estimated duration of use. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification. The hospitalization register comprises all hospitalizations in The Netherlands, including detailed information concerning: the primary and secondary discharge diagnoses; diagnostic, surgical, and treatment procedures; type and frequency of consultations with medical specialists; and dates of hospitalization and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th edition (ICD-9-CM). Hospitals are currently in a transition phase with respect to coding. The objective is that in January 2013, all Dutch hospitals are coding diagnoses according to the ICD-10 (http://www.icd-10.nl/home/-in Dutch). For the current study, all codes are in ICD-9. All PHARMO-linked research is in accordance with Dutch privacy and ethical regulation. The study had no external funding source.

Cohort selection

Community pharmacy records do not contain indications for drug use. However, as the preferred treatment of primary adrenal insufficiency requires suppletion of both glucocorticoids (to replace cortisol) and mineralocorticoids (to replace aldosterone), concurrent use of both drugs is a good marker for the presence of primary adrenal insufficiency. In The Netherlands, most patients with primary adrenal insufficiency are treated with hydrocortisone or cortisone acetate but very few patients are treated with prednisolone instead (6). From the PHARMO RLS, we identified all users of glucocorticoids between January 1998 and December 2008. The theoretical duration of each prescription was assessed by dividing the number of dispensed units by the prescribed daily dose. Prescribed daily doses were subsequently expressed as the number of defined daily doses (DDDs) per day. Primary adrenal insufficiency was defined as concurrent use of glucocorticoids (hydrocortisone, cortisone acetate, or prednisone $\leq$10 mg daily) and mineralocorticoids (fludrocortisone) (6). This definition was required because we aimed to include patients with primary adrenal insufficiency only, thereby excluding patients with secondary adrenal insufficiency. Thus, patients with primary adrenal insufficiency were selected based only on the combination of glucocorticoid and mineralocorticoid usage. No ICD-9 codes were available in this selection. The first date that both types of drugs were used concomitantly marked the start of follow-up. Distinction was made between prevalent and incident patients, where the latter were those patients who were at least 365 days without gluco- and mineralocorticoid usage before the start of the follow-up. The resulting cohort of primary adrenal insufficiency patients was restricted to those who were 18 years or older and had a minimum of two dispensings of glucocorticoids and mineralocorticoids. A reference cohort, about five times the size of the index cohort (n=1933), with the same age and sex distribution was sampled from patients not using glucocorticoids.

Outcome definition

We identified all prescriptions for antibacterial, antiviral, or antifungal medication. For anti-infective agents, episodes were calculated, defined as a cluster of subsequent refills, independent of changes in dose regimen or drug switches within the same class. A new episode was assumed if an interval of 14 days or more occurred between the theoretical end date of one prescription and new prescription. Each episode was considered a separate event. Furthermore, we identified hospital admissions for respiratory (ICD 1–137, 460–466, 480–489, 510, 513), urinary (ICD 580, 590, 595, 597, 599, 601, 604, 614, 615, 616), musculoskeletal (ICD 711, 720, 730), cutaneous (ICD 681, 682), CNS (ICD 320–321), and other (ICD 320–321, 380.1, 381, 382, 324, 421) infections. For this, we used hospital discharge records (ICD-9 codes).

A relapse was defined by a hospital admission for infection occurring during the first 21 days between subsequent hospitalizations. New prescriptions for antibacterial, antiviral, or antifungal medication were not regarded as a new infection when prescribed in the following 14 days after hospital discharge.

Co-morbidity

Several medical conditions are associated with decreased immune response and increased risk of infection. For each subject, presence of diabetes (defined

Table 1 Characteristics of primary adrenal insufficiency patients and controls.

Characteristics	Adrenal insufficiency patients ($n=390$) No. (%)	Control patients ($n=1933$) No. (%)
Sex		
Men	156 (40.0)	775 (40.1)
Women	234 (60.0)	1158 (59.9)
Age (years)		
18–29	40 (10.3)	198 (10.2)
30–39	60 (15.4)	300 (15.5)
40–49	75 (19.2)	367 (19.0)
50–59	68 (17.4)	340 (17.6)
60–69	63 (16.2)	313 (16.2)
70–79	61 (15.6)	302 (15.6)
80+	23 (5.9)	113 (5.9)
Type of glucocorticoid		
Prednisone	34 (8.7)	
<0.67 DDD/day	16	
0.67–1.33 DDD/day	17	
Hydrocortisone	223 (57.2)	
<0.67 DDD/day	20	
0.67–1.33 DDD/day	149	
>1.33 DDD/day	24	
Cortisone acetate	133 (34.1)	
<0.67 DDD/day	7	
0.67–1.33 DDD/day	117	
>1.33 DDD/day	8	
Drugs indicating co-morbidity at cohort entry		
Statins	30 (7.7)	123 (6.4)
Insulin	16 (4.1)	22 (1.1)
Oral antidiabetic drugs	12 (3.1)	72 (3.7)
Thyroid hormone	69 (17.7)	36 (1.9)
Respiratory drugs	34 (8.7)	60 (3.3)
DHEA	4 (1.0)	0 (0.0)

DDD, defined daily doses; <0.67 DDD=<20 mg of hydrocortisone, 0.67–1.33 DDD=20–40 mg of hydrocortisone, >1.33 DDD=>40 mg of hydrocortisone.

by use of insulin and/or oral antidiabetic agents), statins, asthma, chronic obstructive pulmonary disease (COPD) (defined by use of inhalation glucocorticoids), immunodeficiency disorders (defined by use of immunoglobulins and/or immunosuppressants), rheumatoid arthritis, and vasculitis was identified.

Statistical analysis

Incidence rates for infectious events, defined by use of antimicrobial agents, and hospital admission for infection were calculated as the number of infectious events or admissions divided by person-time. Crude incidence ratios (IDRs) and 95% CI were calculated by dividing the incidence rate in the primary adrenal insufficiency cohort by the incidence rate in the control group. Poisson regression analysis was used to adjust for other conditions and drugs associated with an increased risk of infection. We stratified according to age (<40, 40–59, and ≥60 years) and sex. Risk estimates were calculated for all anti-infective drug prescription subtypes, as well as subtypes of hospital admissions for infection. Time-varying analyses, where follow-up time was divided in 90-day periods, were conducted to study the effect of (cumulative) glucocorticoid dose, as well as the frequency of dosing. Data analysis was conducted with STATA, version 10.1, and SPSS version 17.0.

Results

A total of 390 patients met the definition of primary adrenal insufficiency and were included in the primary adrenal insufficiency cohort. The reference cohort consisted of 1933 controls. The cohort characteristics are depicted in Table 1. The use of medication represents co-morbidity at cohort entry, for both newly diagnosed primary adrenal insufficiency and patients with long disease duration. In over 90% of patients in the primary adrenal insufficiency cohort, glucocorticoid replacement was provided by hydrocortisone or cortisone acetate. Only a small proportion of primary adrenal insufficiency patients (1.0%) used DHEA in addition to gluco- and mineralocorticoids. The prevalence of insulin use, thyroid hormone replacement therapy, and use of respiratory drugs was statistically significantly higher in the primary adrenal insufficiency cohort compared with the reference cohort.

The incidence of infectious events was 59.2/100 person-years in the primary adrenal insufficiency cohort, about one and a half times the rate in the reference cohort (34.8/100 person-years; crude incidence rate ratio (IRR) of 1.61, 95% CI 1.51–1.72). Adjustment for age, sex, co-medication, and co-morbidity had only marginal effects on the risk estimate: adjusted IRR 1.58 (95% CI 1.47–1.70). IRRs were consistently increased across anti-infective drug prescription subtypes (Table 2). The highest risk estimates were found for antifungal and antiviral drugs with adjusted IRRs of 1.99 (95% CI 1.46–2.72)

Table 2 Incidence rates of infectious episodes according to antimicrobial drug prescription in primary adrenal insufficiency and reference cohort.

	Number of episodes	Rate/100 person-years	Crude IRR (95% CI)	Adjusted IRR (95% CI)[a]
Antibacterial				
Reference	3340	34.8	1	1
Addison	1157	55.0	1.58 (1.48–1.69)	1.56 (1.45–1.68)
Antifungal				
Reference	159	1.6	1	1
Addison	67	3.2	1.98 (1.47–2.65)	1.99 (1.46–2.72)
Antiviral				
Reference	38	0.4	1	1
Addison	18	0.9	2.23 (1.27–3.90)	1.99 (1.05–3.79)

IRR, incidence rate ratio.
[a]Adjusted for age, sex, insulin, inhalation glucocorticoids, COPD.

Table 3 Hospital admissions for infection.

	Admissions	Rate/100 person-years	Crude IRR (95% CI)	Adjusted IRR (95% CI)[a]
All cause				
Reference	79	0.8	1	1
Addison	80	3.8	5.02 (3.66–6.87)	4.34 (3.04–6.22)
Respiratory infections				
Reference	19	0.2	1	1
Addison	40	1.9	9.9 (5.73–17.09)	8.25 (4.52–15.07)
Pneumonia				
Reference	14	0.1	1	1
Addison	30	1.4	10.08 (5.34–19.00)	9.42 (4.91–18.05)
Urinary tract infections				
Reference	13	0.1	1	1
Addison	11	0.5	3.98 (1.78–8.88)	4.56 (2.03–10.25)

IRR, incidence rate ratio.
[a]Adjusted for age, sex, insulin, inhalation glucocorticoids, COPD.

and 1.99 (95% CI 1.05–3.79) respectively. Stratification according to age showed the highest IRRs among primary adrenal insufficiency patients aged 60 years and older. The incidence of serious infection events requiring hospital admission was five times higher among patients with primary adrenal insufficiency compared with controls (3.8/100 vs 0.8/100 person-years). For subtypes of infection, the rates for pneumonia and urinary tract infection were respectively more than nine and four times higher in primary adrenal insufficiency patients compared with controls (Table 3).

Subsequently, we stratified the primary adrenal insufficiency cohort in prevalent and incident patients, where an incident primary adrenal insufficiency patient was defined by no history of gluco- and mineralocorticoid usage before the index date. In general, incidence rates were marginally higher in incident cases compared with prevalent primary adrenal insufficiency patients (data not shown). Furthermore, we explored within the primary adrenal insufficiency cohort whether the presence of an additional autoimmune disorder would lead to an increased risk of infection. Patients with both primary adrenal insufficiency and type 1 diabetes mellitus had a twofold increased risk of an infectious event (adjusted IRR 2.00, 95% CI 1.52–2.65) and a more than threefold increased risk of admission for infection (adjusted IRR 3.53, 95% CI 1.42–8.8) compared with patients having primary adrenal insufficiency alone. In a similar analysis for thyroid disease, no differences were found. Assessment of seasonal differences in the occurrence of infectious events showed that highest risk estimates were observed during the winter months.

In order to study the effect of glucocorticoid dosage on infection risk, we performed time-varying analysis, classifying patients in three cumulative dosage groups based on tertiles of cumulative dose. No obvious effect of cumulative dose on the risk of infectious events was found with adjusted IRRs for the medium and high cumulative dose compared with low cumulative dose of 1.64 (95% CI 1.25–2.16) and 1.42 (95% CI 1.05–1.97) respectively. To study potential effects on fluctuating levels during the day, we assessed the influence of the frequency of glucocorticoid dosing. No differences in infection risk were found for patients on a once-daily regimen vs patients using glucocorticoids multiple times daily (data not shown).

Discussion

In this cohort study, we found that the risk of infectious episodes, defined by the use of antimicrobial agents, among patients with primary adrenal insufficiency was 1.5 times higher and the risk of hospital admission as a result of infection was 4.5 times higher compared with sex- and age-matched controls. To our knowledge, this is the first study to report on increased risk of infections in patients with primary adrenal insufficiency.

It is unclear whether the observed association between primary adrenal insufficiency and infectious events is related to adrenal replacement therapy or the underlying disease itself. Primary adrenal insufficiency patients are treated with low-dose glucocorticoids for life. Glucocorticoid replacement therapy cannot mimic normal physiology, and as a result, over replacement frequently occurs, which ultimately leads to high cumulative dosages. The fact that the incidence of antifungal and antiviral drug prescriptions is higher than antibacterial drugs, prescriptions suggest a defect in the adaptive cellular immunity, a well-known side effect of glucocorticoids (7, 8). Stuck *et al.* (9) evaluated the risk of infectious complications in patients taking glucocorticoids. In a meta-analysis of 71 trials involving over 2000 patients with different diseases and different dosages, they found that infection rates were significantly increased in patients given an average dose of prednisone of more than 10 mg/day or a cumulative dose of >700 mg. Our results do not support the hypothesis that the cumulative dose of glucocorticoids in patients with primary adrenal insufficiency is associated with the increased risk of infection, given the absence of a clear dose–effect relationship. We speculate that the substitution dosage used in primary adrenal insufficiency, although leading to somewhat higher average cortisol concentrations throughout the day, probably does not lead to an increased risk of infection as seen in patients treated with high pharmacological glucocorticoid dosages. This is further supported by our finding that frequency of daily dosing did not seem to have an effect on infection risk.

The increased risk of infectious episodes already present in incident primary adrenal insufficiency patients suggests that other factors like decreased resistance to infections in the scope of (active)

autoimmunity could play a role. Diabetes mellitus type 1, a comparable endocrine autoimmune disease, has also been associated with increased rates of infections (10). This is partially due to defects in cellular innate immunity such as decreased chemotaxis, phagocytosis of polymorphonuclear cells, monocytes, and macrophages (11). Studies on defects in immunity in patients with Addison's disease are lacking.

A speculative alternative explanation for the increased infection risk in autoimmune adrenalitis and some types of congenital adrenal hyperplasia (CAH) could be DHEA deficiency. There is evidence that DHEA may play a role as a regulator of immune function (12). DHEA has been shown to enhance immune function directly by regulating cytokine production and immune cell cytotoxicity as well as to have indirect benefits by counteracting the immune suppressive effects of glucocorticoids. In our adrenal insufficiency cohort, only 1% of patients used DHEA replacement. Laboratory results on DHEA and DHEAS were not available to us. This would have enabled us to speculate more on the role of DHEA in the increased risk of infection.

Several studies have shown an increased risk of infection in patients with diabetes mellitus (10, 13). Our results are in line with these findings, as we found a twofold increased risk of infectious events and a more than threefold increased admission risk for infection in patients with both primary adrenal insufficiency and diabetes mellitus compared with patients with primary adrenal insufficiency alone.

The strengths of this study are its population-based nature, the substantial sample size, and the reliable longitudinal data collection on both drug exposure and hospitalization. There are some limitations as well. As we had no data on medical diagnoses, identification of patients with primary adrenal insufficiency was based on pharmacy records only, which could have resulted in misclassification. Due to the selection of patients using both glucocorticoids and mineralocorticoids, it is possible that a small number of patients with primary adrenal insufficiency not using mineralocorticoids were missed, but we expect this to be a very small number as primary adrenal insufficiency patients in The Netherlands are mainly treated with the combination of glucocorticoids and mineralocorticoids. The patients among our prevalent primary adrenal insufficiency cohort are in fact patients with different types of primary adrenal insufficiency such as autoimmune adrenalitis, salt-wasting CAH, or patients after bilateral adrenalectomy. In the incident Addison cohort, however, probably no salt-wasting adrenogenital syndrome patients are included because we excluded patients under the age of 18 and the vast majority of adult patients with adrenogenital syndrome are being treated with dexamethasone instead of hydrocortisone or cortisone acetate (14).

A limitation of our study might be diagnostic suspicion bias. It could be that general practitioners and medical specialists are more likely to initiate treatment or admit patients with primary adrenal insufficiency to hospital under suspicion of infection due to a fear of a potential adrenal crisis in case of stress and disease. This could have resulted in an overestimation of observed effect. However, admission rates were based on discharge records after thorough diagnosis and treatment in the course of the disease. In addition, Dutch physicians have a renowned low tendency to treat patients with antimicrobial drugs to decrease the risk of resistance, treating only patients with a proven or very high suspicion of infection (15).

In conclusion, our results show an increased use of antimicrobial agents and infection-related hospital admissions in patients with primary adrenal insufficiency compared with controls. In order to gain more insight into the possible increased risk of infections in patients with primary adrenal insufficiency, likely underlying causes of increased risk of infection should be studied. In addition, the potential positive effects of DHEA replacement and preventive strategies such as vaccination on the incidence of infections should be explored in future studies.

Declaration of interest

All authors declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work and no other relationships or activities that could appear to have influenced the submitted work.

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