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The risk of affective disorders in patients with adrenocortical insufficiency

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Summary *Objective*: To investigate the risk of affective disorders among patients hospitalised with adrenocortical insufficiency in the study period: 1977–1999.
Method: Using data from Danish registers, two study cohorts were identified by their ICD diagnoses at discharge from hospital: one comprising all patients with a first hospital admission with an index diagnosis of adrenocortical insufficiency; the other a control cohort comprising all patients with a first hospital admission with an index diagnosis of osteoarthritis. Subsequent admissions to psychiatric hospital wards with discharge ICD diagnoses of affective disorders were used as events of interest. Rates of readmission were estimated using Poisson regression models in survival analyses. Age, sex, duration of time after index discharge, and calendar time were included as co-variables. The primary analysis included all patients with adrenocortical insufficiency. Thereafter, the subgroup of patients with primary adrenocortical insufficiency (Addison's disease) was investigated separately in a secondary analysis.
Results: A study sample of 989 patients with adrenocortical insufficiency and 124,854 patients with osteoarthritis was identified. Eight hundred and fifty-two patients were subsequently readmitted with a diagnosis of affective disorder. Patients with adrenocortical insufficiency had a 2.68 (95% CI: 1.62–4.42) times greater rate of affective disorders and a 2.12 (95% CI: 1.16–3.86) times greater rate of depressive disorder when compared with the rate for patients with osteoarthritis. Patients with Addison's disease had a 2.14 (95% CI: 1.14–4.03) times greater rate of affective disorders, and a 1.71 (95% CI: 0.81–3.63) times greater rate of depressive disorder compared with the rate of patients with osteoarthritis.
Conclusion: Patients with adrenocortical insufficiency may be at increased risk of developing severe affective disorders. Conventional replacement therapy with hydrocortisone may not be sufficient to ensure the psychiatric well-being of these patients.

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1. Introduction

There are relatively many investigations of Cushing's disease and the effect of hypercortisolemia on brain function and mood regulation, but few on the neuropsychiatric consequences of adrenocortical insufficiency and the resulting hormone deficiencies. Most existing studies of the neuropsychiatric symptoms of Addison's disease are retrospective case series predating contemporary criteria for description and diagnosis of psychiatric disorders (Starkman, 2003). Formerly, it was believed that glucocorticoid replacement is an effective treatment for the psychiatric symptoms that patients with Addison's disease exhibit on presentation, and that continuous replacement therapy ensures normal physical and psychological functioning (Money and Jobaris, 1977; Leigh and Kramer, 1984; Johnstone et al., 1990); however, recent epidemiological studies and studies of hydrocortisone and dehydroepiandrosterone (DHEA) replacement strategies suggest that patients may have persistent mental health reduction, lack of energy, and reduced quality of life (Arlt and Allolio, 2003).

The physiological role of DHEA is unclear, but abnormal levels of DHEA are seemingly associated with chronic conditions where mood and well-being are often affected (Finset et al., 2004; Cleare et al., 2004; Boscarino, 2004). DHEA may have a significant antidepressant effect in patients with major depression (Wolkowitz et al., 1999; Schmidt et al., 2005). Patients with adrenocortical insufficiency have decreased production of DHEA, and although results are divergent, studies of the effects of DHEA supplementation suggest that patients with adrenocortical insufficiency have increased fatigue, and a decreased sense of well-being, general health and vitality (Arlt et al., 1999; Hunt et al., 2000; Lovas et al., 2003). It may be that mood is also negatively affected. Whether these impairments are associated with long-term mood changes of clinical severity is unknown.

Adrenocortical insufficiency is a rare condition, and no prospective study of mental status during replacement therapy with different doses of hydrocortisone, or during supplementation with DHEA, included more than 40 patients or used a follow-up time of more than 1 year. Some of the studies investigated mood symptoms in patients with both primary- and secondary adrenocortical insufficiency. Patients with these syndromes may exhibit different disturbances in hypothalamic–pituitary–adrenal (HPA) axis regulation, and those with secondary adrenocortical insufficiency often have additional deficiencies in other hormone systems, which may put them at greater risk of mood disorders than patients with primary adrenocortical insufficiency (Addison's disease).

In view of the lack of controlled, long-term studies, we found it relevant to investigate the risk of developing mood disorders in a cohort of patients with adrenocortical insufficiency with an approach that enabled us to follow many patients over a lengthy period.

Using data available in the Danish patient registers, we conducted a cohort study with delayed entry into cohorts. We compared the risks for patients with hospital diagnoses of adrenocortical insufficiency or of osteoarthritis of receiving diagnoses of affective disorders on readmission to hospital. We investigated all patients with adrenocortical insufficiency diagnoses in a primary analysis. Thereafter, a subgroup of these patients with diagnoses of Addison's disease was investigated in a secondary analysis. We hypothesised that patients hospitalised with adrenocortical insufficiency would have a higher incidence of negative mood disturbances, and hence a higher risk of hospitalisation with diagnoses of depressive disorder than control patients with osteoarthritis, and that this risk would be increased both for all patients with adrenocortical insufficiency and for the subgroup of patients with Addison's disease. Because patients with adrenocortical insufficiency are treated with exogenous glucocorticoids, we also expected to find a higher relative risk of mania/bipolar disorder diagnoses among these patients. We used hospitalised control patients in order to reduce the impact of Berksons bias on the estimated rates of affective disorder hospitalisations (Berkson, 1946).

2. Methods

2.1. Danish register data

We obtained data from three Danish registers after approval from the Danish Data Protection Agency.

In Denmark, hospital admissions to psychiatric wards have been recorded in a nationwide register, the Danish Psychiatric Central Research Register (DPCRR) (Munk-Jorgensen and Mortensen, 1997) since 1 April 1970. From 1 April 1970 to 31 December 1993, the Danish edition of the International Classification of Diseases 8 (ICD-8) was used for registration (WHO, 1971). Since 1 January 1994, the updated International Classification of Diseases 10, ICD-10, has been in use (WHO, 1993).