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REVIEW
MANAGEMENT OF ENDOCRINE DISEASE

The burden of Cushing's disease: clinical and health-related quality of life aspects

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Abstract

Objective: Cushing's disease (CD) is a rare endocrine disorder characterized by excess secretion of ACTH due to a pituitary adenoma. Current treatment options are limited and may pose additional risks. A literature review was conducted to assess the holistic burden of CD.
Design: Studies published in English were evaluated to address questions regarding the epidemiology of CD, time to diagnosis, health related quality of life (HRQoL), treatment outcomes, mortality, prevalence of comorbidities at diagnosis, and reversibility of comorbidities following the treatment.
Methods: A two stage literature search was performed in Medline, EMBASE, and Science Citation Index, using keywords related to the epidemiology, treatment, and outcomes of CD: i) articles published from 2000 to 2012 were identified and ii) an additional hand search (all years) was conducted on the basis of bibliography of identified articles.
Results: At the time of diagnosis, 58 85% of patients have hypertension, 32 41% are obese, 20 47% have diabetes mellitus, 50 81% have major depression, 31 50% have osteoporosis, and 38 71% have dyslipidemia. Remission rates following transsphenoidal surgery (TSS) are high when performed by expert pituitary surgeons (rates of 65 90%), but the potential for relapse remains (rates of 5 36%). Although some complications can be partially reversed, time to reversal can take years. The HRQoL of patients with CD also remains severely compromised after remission.
Conclusions: These findings highlight the significant burden associated with CD. As current treatment options may not fully reverse the burden of chronic hypercortisolism, there is a need for both improved diagnostic tools to reduce the time to diagnosis and effective therapy, particularly a targeted medical therapy.

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Introduction

Cushing's disease (CD) is a rare condition caused by a pituitary adenoma that secretes excess ACTH (1), which promotes excess cortisol production from the adrenal glands. Excess cortisol induces a clinical phenotype that harbors all components of the metabolic syndrome, such as central obesity, diabetes mellitus, dyslipidemia, and hypertension, as well as muscle weakness, hirsutism, increased bruisability, psychological dysfunction, and osteoporosis (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11).

Patients with CD experience a significant clinical burden due to comorbidities, increased mortality, and impaired health-related quality of life (HRQoL) due to prolonged exposure to elevated cortisol levels (3, 5, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20). In particular, patients with CD often experience severe fatigue and weakness, physical changes, emotional instability, depression, and cognitive impairments, which have a profound impact on daily life (13, 21).

Although there have been several consensus statements published recently on the definition of remission, diagnosis, and the management of CD, the severity and diversity of the clinical scenario and associated morbidities continue to present a management challenge (1, 22, 23). Additionally, there is recent evidence of persistent deleterious effects after remission, most notably persistent elevated cardiovascular risk (3, 22). The main objective of the current literature review is to describe the current burden of the disease and to summarize data on specific aspects of this burden, which underscores the need for improved diagnostic and therapeutic approaches.

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Materials and methods

Available literature were evaluated to address questions regarding the epidemiology of CD, time to diagnosis, mortality, prevalence of comorbidities at diagnosis, reversibility of comorbidities after treatment (in particular, after disease remission), outcomes and complications of current treatment options, and HRQoL associated with CD and interventions.

The literature search was performed in Medline, EMBASE, and Science Citation Index, using keywords related to the epidemiology, treatment, and outcomes of CD. It was conducted in two stages: i) articles published between 2000 and 2012 were identified through a PubMed search using the following keywords: CD, incidence, prevalence, mortality, treatment, remission, cure, excess cortisol, outcomes, cost, QoL, morbidities, transsphenoidal surgery (TSS), adrenalectomy, radiotherapy, steroidogenesis inhibitors, ketoconazole, mitotane, aminoglutethimide, etomidate, metyrapone, pasireotide, and cortisol receptor antagonists; and ii) an additional hand search was conducted on the basis of the bibliographies of identified articles. All studies that provided data (regardless of publication year) related to these research questions were retained.

Definitions

Different criteria for defining the remission of hypercortisolism have been proposed, ranging from the occurrence of definitive or transient postoperative hypocortisolemia to the adequate suppression of cortisol after dexamethasone administration. According to a recent consensus statement (23), persistent postoperative morning serum cortisol levels of <2 μg/dl ($\sim$50 nmol/l) are associated with remission and a low recurrence rate of $\sim$10% at 10 years. Persistent serum cortisol levels above 5 μg/dl ($\sim$140 nmol/l) for up to 6 weeks following surgery require further evaluation. When serum cortisol levels are between 2 and 5 μg/dl, the patient can be considered in remission and can be observed without additional treatment for CD. A subset of patients can even develop complete adrenal insufficiency (serum cortisol levels below 2 μg/dl ($\sim$50 nmol/l)) up to 12 weeks postsurgery (24, 25). Therefore, repeated evaluation in the early postoperative period is recommended. However, long-term follow-up is necessary for all patients because no single cortisol cutoff value excludes those who later experience disease recurrence, and up to 25% of patients develop a recurrent adenoma within 10 years after surgery (26, 27, 28).

Results

Incidence and prevalence of CD

Although epidemiologic data on CD are limited, several population-based studies indicate an incidence of 1.2–2.4 per million (14, 19) and the prevalence of diagnosed cases to be $\sim$39 per million population (14). Lindholm *et al.* (19) used the case definition as either the presence of a corticotroph adenoma or remission after neurosurgery, which yielded an estimated incidence rate of 1.2–1.7 per million per year. Etxabe & Vazquez (14) reported an incidence of 2.4 per million in Vizcaya, Spain. A large-scale retrospective survey carried out in New Zealand by Bolland *et al.* (29) found the approximate prevalence of all forms of Cushing's syndrome (CS) (the majority of these cases were of pituitary origin) to be 79 per million and the incidence to be 1.8 per million per year. Differences in epidemiologic estimates may be attributable to varying case definitions (for instance, the study by Lindholm excluded cases in which the adenoma could not be localized or those that could not achieve remission from surgery), geographical differences, and temporal effects. The prevalence of CD may be underestimated due to unrecognized patients with mild symptoms and patients with a cyclic form of CD (30).

Time to diagnosis

Data on the time from onset of symptoms to diagnosis are also limited. In a prospective study by Flitsch *et al.* (31) of 48 patients with pituitary adenomas, including 19 who had ACTH-secreting adenomas causing CD, the reported time from onset of symptoms to diagnosis was 4.3 years. A study by Martinez Ruiz *et al.* (32), which was based on only four pediatric CD patients, reported the time between onset of symptoms and diagnosis as ranging from 2.5 to 5 years. Etxabe & Vazquez (14) estimated that the average time from onset of clinical symptoms to diagnosis in 49 CD patients was 45.8 ± 2.7 months (6–144 months), thus 3.8 years. This is corroborated by the findings from a Belgian cross-sectional study on pituitary adenomas including CD, which estimated that patients experienced symptoms for an average of 45 months before diagnosis (33). However, the reliability and generalizability of these data are limited by small sample sizes and the retrospective nature of the studies. Indeed, the New Zealand data from Bolland *et al.* (29) report that on presentation, patients experienced symptoms for a median of 2.0 years (but ranging up to 20 years) before diagnosis. On the basis of data from the prospective European Registry on Cushing's syndrome (ERCUSYN) (total number of patients 481, of whom 66% of patients had CD), median delay in diagnosis was 2 years (34).

Mortality in patients with CD

Mortality in patients with CD has been analyzed in several small studies, with overall rates reported as standardized mortality ratio (SMR) ranging from 1.7 to 4.8 (Table 1) (14, 15, 17, 19). In studies in which mortality was assessed among those in remission and

Table 1 Mortality in patients with CD.

Study design	*n*	**SMR** (95% CI)	Comments
Population-based study 18-year follow-up (14)	49	3.8 (2.5 17.9)	SMR of vascular disease was 5.0. Older age, persistence of hypertension, and abnormalities of glucose metabolism after treatment were independent predictors of mortality
Retrospective study Follow-up 1981 1996 (17)	74 CS 48 CD	1.68 (0.8 30.9)	Mortality risk was moderately increased compared with that of the general population
National Patient Registry study 11-year period (19)	166 CS 73 CD	3.68 (2.34 5.33) 1.7 (with proven etiology)	The authors in this study reported excess mortality in the first year after diagnosis. After the first year, mortality was not significantly higher than that of the background population
Single-center study. Mean duration of follow-up was 10.1±7.2 years for the whole cohort (15)	248	2.39 (1.22 3.9)	The SMR in patients with CD with remission after TSS was 1.80 (95% CI: 0.71 3.37), whereas the SMR in patients with persistent disease was 4.38 (95% CI: 1.38 9.07)
Single-center study. Median duration of follow-up was 15 years (36)	60	4.8 (2.8 8.3)	Vascular disease SMR: 13.8 (95% CI: 7.2 36.5). SMR for persistent disease (n=6): 16 (95% CI: 6.7 38.4) vs remission (n=54): 3.3 (95% CI: 1.7 6.7)
Systematic review and meta-analysis (40)	7 studies	1.84 (1.28 2.65)	SMR for persistent disease after surgery 3.73 (95% CI: 2.31 6.01)
Single-center study (38)	80	3.17 (1.70 5.43)	Cure group SMR 2.47 (95% CI: 0.80 5.77) Recurrent/persistent disease group SMR: 4.12 (95% CI: 1.12 10.54)
Nationwide retrospective survey (29)	253 CS; 158 (62.4%) microadenoma; 30 (11.9%) macroadenoma	Macroadenoma: 3.5 (1.3 7.8); microadenoma: 3.2 (2.0 4.8)	In all 253 patients with CS: SMR 4.1 (95% CI 2.9 5.6)

those with persistent disease separately, patients with persistent hypercortisolemia consistently had the highest mortality risk (15, 19, 35, 36). In addition, TSS as a first-line treatment has been an important advance as high remission rates after initial surgery have been accompanied by mortality rates that mirror those observed in the general population (17, 35, 37). In a case series from the UK, it was found that the majority of deaths occurred before 1985, which was before TSS was employed as the routine first-line treatment at the center (36). In a recent retrospective study, 80 patients undergoing TSS for CD between 1988 and 2009 were evaluated, and long-term cure (defined as ongoing absence of hypercortisolism at last follow-up) was reported in 72% of patients. However, overall elevated mortality persisted in patients (SMR 3.17 (95% CI: 1.70–5.43)), including those who achieved 'cure' (SMR 2.47 (95% CI: 0.80–5.77)), although even higher mortality was seen in those with postoperative recurrence/persistent disease (SMR 4.12 (95% CI: 1.12–10.54) (38). Additionally, a nationwide, retrospective study in New Zealand reported significant persistently increased mortality both in macro- and microadenomas (SMR 3.5 (1.3–7.8) and 3.2 (2.0–4.8) respectively), despite long-term biochemical remission rates of 93 and 91% of patients, respectively (29).

In a single-center study designed to assess the impact of hypercortisolism vs the occurrence of a pituitary adenoma in mediating increased mortality risk, patients with CD had higher mortality rates than patients with nonfunctioning pituitary macroadenomas (SMR 2.4 vs 1.4) (15). Patients with persistent hypercortisolism after initial TSS had the highest elevated mortality (SMR 4.4) (15), which suggests that hypercortisolism and the length of exposure to hypercortisolism is associated with increased mortality. This finding is similar to the results of a Danish population study in which patients with persistent hypercortisolism after initial surgery had an SMR of 5 (19). Some deleterious effects of excess cortisol exposure appear to persist as even patients who achieved surgical remission still had elevated mortality (SMR 1.8) (15). Patients with possible CD but whose disease etiology was unproven had the highest reported mortality risk in the literature (SMR 11.5) (19). Among these patients, etiology could not be confirmed because the adenoma could not be localized, patients were unable to achieve remission after surgery, or patients died before a full clinical workup could be done (19).

Mortality has been reported to be higher in females (SMR 4.5) (14), particularly from vascular causes (SMR 5), although it is important to note that this study had a 15:1 female to male preponderance and other studies have not observed gender differences in mortality (14, 19). However, questions remain regarding the relationship between specific dimensions of hypercortisolism in CD, such as the duration of exposure to hypercortisolism and the severity of this exposure, and mortality.

Patients with CD are most likely to die from cardiovascular or cerebrovascular causes (14, 15, 19, 37). In the study by Dekkers *et al.* (15), the leading causes of death were cardiovascular disease (23.4%), cerebrovascular disease (12.8%), malignancy (19%), and infectious diseases (17%). Additionally, the average age at death in this Dutch study was reported to be 62.4 years, which is significantly lower than the life expectancy of the general population (80 years) (9, 39). Similarly, Hassan-Smith *et al.* (38) reported that the leading causes of death were cardiovascular disease (n 8), cancer (n 3), infection (n 1), and CD (n 1), with the median age at death being 57 years. A recent systematic review and meta-analysis of mortality in patients with CS drawing from seven studies estimated that the SMR for patients with CD is 1.84 (95% CI: 1.28–2.65), with patients with persistent disease after surgery having an SMR of 3.73 (95% CI: 2.31–6.01) (40).

These conclusions drawn from small studies and case series with a low number of deaths and variable follow-up time should be interpreted with caution. Studies with longer follow-up time and more analyzable events are needed to assess whether long-term mortality is normalized after long-term remission or whether persistent cardiovascular risk factors translate into an increased mortality risk. The fact that some studies have shown persistent elevated mortality after cure, in particular the study by Hassan-Smith *et al.* (38) where all patients underwent TSS, may suggest that a stricter definition of 'cure' could be applied. Nonetheless, these findings suggest that normalization of cortisol secretion improves mortality, but may be insufficient to normalize mortality as other factors, like adverse cardiovascular risk factors or hypopituitarism, may determine the mortality outcome of patients after successful surgery. In the large retrospective survey from New Zealand, demographic predictors of mortality in patients with a micro- or macroadenoma were older age, hypertension, and diabetes mellitus. It is of note that patients with an adrenal adenoma (n 37) had an elevated SMR but very good prognosis following the treatment (29). This may suggest that pituitary compromise may account for the persistent elevated mortality in patients with 'cured' disease following transsphenoidal intervention. The data reported by Bolland *et al.* (29) also showed a relatively consistent elevated SMR over four time periods (1960–1980, 1980–1990, 1990–2000, and 2000–present) despite a general shift in pituitary-directed therapy from radiotherapy to TSS, which is at odds with the previously discussed UK data in which the majority of deaths occurred before 1985, before TSS was employed as the standard first-line therapy (36). Nonetheless, early detection and rapid intervention may be key in avoiding long-term sequelae of the disease (41). As CD is a rare disease and, thus, difficult to study, it is hoped that databases such as the ERCUSYN, which now includes more than 500 patients, could become a key resource to further research and aid collaboration (42).

It should be noted that geographic variability in time to diagnosis, the availability of pituitary experts, and the awareness levels of general practitioners who may first encounter patients with undiagnosed CD can all lead to treatment disparities and differences in remission and mortality rates between countries and regions.

Comorbidities: prevalence and reversibility

The chronic hypersecretion of cortisol causes central obesity, systemic arterial hypertension, impaired glucose tolerance, dyslipidemia, and hypercoagulability, and is associated with other comorbidities, such as psychological and cognitive dysfunction, osteoporosis, and increased susceptibility to infection (1, 9, 43, 44) (Table 2 and Supplementary Table 1, see section on supplementary data given at the end of this article). When compared with the general population, CD patients showed a greater than twofold increase in hypertension, diabetes, and osteoporosis, and an increase of over five times the rate of major depression and impaired glucose tolerance (Fig. 1) (45, 46, 47). A recent study, using whole-body magnetic resonance imaging (MRI), evaluating body composition and cardiovascular parameters after remission of CD found that cardiovascular risk persisted despite potential dramatic improvements in body composition abnormalities (48).

Cardiovascular complications Among all systemic consequences of hypercortisolism, cardiovascular complications are the most dire as these are among the leading causes of death in patients with CD (14, 15). Cardiovascular risk is increased in CD due to complications such as hypertension, atherosclerosis, hypercoagulability, obesity, diabetes, and dyslipidemia, which are all consequences of chronic cortisol hypersecretion (1, 49). In addition, CD is associated with left ventricular hypertrophy and diastolic dysfunction (50).

Years after disease remission, cardiovascular morbidity persists (3, 51). However, despite numerous studies determining the cardiovascular risk in the general population, there are few studies that comprehensively evaluate the cardiovascular risk factors and assess the global risk for patients with CD. A recent paper by De Leo *et al.* (52) suggests that assessing the global

Table 2 Comorbidities, prevalence at diagnosis, and reversibility in patients with CD.

Morbidity	Prevalence at diagnosis	Reversibility
Hypertension	55 85% (12, 14, 22, 53)	18-Year follow-up: posttreatment 24% (12/49); diagnosis 55% (27/49) (14) After 5 years' cortisol normalization: CD 40% (6/15); BMI-matched controls 20% (6/30) (3) After 1 year's cortisol normalization, hypertension was reversed in 44% (12) Less than 2 years after successful remission, 75% had normalized BP (55)
IGT	21 64% (12, 14, 22, 53)	18-Year follow-up: posttreatment 4% (2/49); diagnosis 24% (12/49) (14) After 5 years' cortisol normalization: CD 27% (4/15); BMI-matched controls 27% (8/30) (3)
Diabetes mellitus	20 47% (12, 14, 22, 53)	18-Year follow-up: posttreatment 18% (9/49); diagnosis 39% (19/49) (14) After 5 years' cortisol normalization: CD 33% (5/15); BMI-matched controls 7% (2/30) (3) After 1 year's cortisol normalization, diabetes was reversed in 40% of patients (12)
Overweight (BMI 25 30 kg/m^2)	21 48% (12, 22, 53)	After 5 years' cortisol normalization: CD 33% (5/15); sex- and age-matched controls 20% (6/30) (3)
Obesity (BMI > 30 kg/m^2)	32 41% (12, 22, 53)	After 5 years' cortisol normalization: CD 40% (6/15); 0 in controls (3) After 1 year's cortisol normalization, 38% were no longer obese (12)
Dyslipidemia	38 71%[a] (22, 53)	After 5 years' cortisol normalization, the prevalence was 27% (3)
Hypercoagulopathy/hemostatic abnormalities	Hemostatic abnormalities (53.6%) (53) Vascular morbidity (10%) (49) VTE (incidence 2.5 3.1 per 1000 persons per year) (57)	Adequate prophylaxis with anticoagulants can reverse the prothrombotic state and greatly reduce the risk of postoperative thromboembolic events (49)
Kidney disease	Nephrolithiasis: 50% (116)	Prevalence in patients achieving remission 27% (116)
Osteoporosis/compression fractures	Osteoporosis: 38 50% (6, 71) Fractures[b]: 15.8% (71)	Only partially reversible 2 years after normalization of cortisol levels (67)
Major depression/psychopathology[c]	MDD/MD/MAD: 54 81% (10, 72, 73) Overall psychopathology: 67% (5) Atypical depression: 51.5% (5)	Prevalence of MD at 3 months: 54%; at 6 months: 36%; at 12 months: 24% (5) About 70% of patients fully recovered from their depression (75)
Cognitive deficits/loss of brain volume	Subjective loss of brain volume: 86% (80)	Partially reversible (based on retrospective study in 38 patients only) (80)

BP, blood pressure; IGT, impaired glucose tolerance; MAD, major affective depression; MD, major depression; MDD, major depressive disorder; VTE, venous thromboembolism.
[a]Lipid profile abnormalities (combined increased cholesterol and triglycerides 25%).
[b]Pituitary Cushing's.
[c]Psychopathology includes atypical depression, major depressive disorder, and other psychiatric disorders.

cardiovascular risk and managing the risk associated with cardiovascular disease such as hypertension, obesity, glucose intolerance, insulin resistance, dyslipidemia, endothelial dysfunction, and the hypercoagulable state should be the important goals of treatment for CD.

Hypertension Hypertension has been reported in 55–85% of patients with CD, with most cases being mild to moderate (3, 12, 14, 22, 53). Hypertension remits in a subset of patients (44–75%, Table 2) after successful treatment but persists in ~24–56% (12, 14, 22), presumably due to microvessel remodeling or concomitant underlying essential hypertension (54). The duration of disease has been shown to be longer in hypertensive patients (4.8 ± 3.7 years) than in normotensive (0.7 ± 0.2 years) patients (22) and has been identified as a significant risk factor in several studies (54, 55). Older age and longer duration of hypertension before treatment also negatively influenced the normalization of high blood pressure after resolution of hypercortisolism.

Hypercoagulopathy Patients with CD show various abnormalities of hemostatic parameters and those with active CD show an increased thrombotic tendency (56). Increased cortisol levels stimulate the synthesis of several clotting factors, such as fibrinogen by the liver and von Willebrand factor by endothelial cells. Glucocorticoids also upregulate the synthesis of plasminogen activator inhibitor type 1, the main inhibitor of the fibrinolytic system (49). This hypercoagulability state is a crucial factor predisposing CD patients to thromboembolic events, mostly after surgery and during inferior

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