The Treatment of Cushing's Disease

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Cushing's disease (CD), or pituitary-dependent Cushing's syndrome, is a severe endocrine disease caused by a corticotroph pituitary tumor and associated with increased morbidity and mortality. The first-line treatment for CD is pituitary surgery, which is followed by disease remission in around 78% and relapse in around 13% of patients during the 10-year period after surgery, so that nearly one third of patients experience in the long-term a failure of surgery and require an additional second-line treatment. Patients with persistent or recurrent CD require additional treatments, including pituitary radiotherapy, adrenal surgery, and/or medical therapy. Pituitary radiotherapy is effective in controlling cortisol excess in a large percentage of patients, but it is associated with a considerable risk of hypopituitarism. Adrenal surgery is followed by a rapid and definitive control of cortisol excess in nearly all patients, but it induces adrenal insufficiency. Medical therapy has recently acquired a more important role compared to the past, due to the recent employment of novel compounds able to control cortisol secretion or action. Currently, medical therapy is used as a presurgical treatment, particularly for severe disease; or as postsurgical treatment, in cases of failure or incomplete surgical tumor resection; or as bridging therapy before, during, and after radiotherapy while waiting for disease control; or, in selected cases, as primary therapy, mainly when surgery is not an option. The adrenal-directed drug ketoconazole is the most commonly used drug, mainly because of its rapid action, whereas the glucocorticoid receptor antagonist, mifepristone, is highly effective in controlling clinical comorbidities, mainly glucose intolerance, thus being a useful treatment for CD when it is associated with diabetes mellitus. Pituitary-directed drugs have the advantage of acting at the site responsible for CD, the pituitary tumor. Among this group of drugs, the dopamine agonist cabergoline and the somatostatin analog pasireotide result in disease remission in a consistent subgroup of patients with CD. Recently, pasireotide has been approved for the treatment of CD when surgery has failed or when surgery is not an option, and mifepristone has been approved for the treatment of Cushing's syndrome when associated with impairment of glucose metabolism in case of the lack of a surgical indication. Recent experience suggests that the combination of different drugs may be able to control cortisol excess in a great majority of patients with CD. **(*Endocrine Reviews* 36: 385–486, 2015)**

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I. Introduction

Cushing's disease (CD), or pituitary-dependent Cushing's syndrome (CS), is the most common form of endogenous CS, accounting for around 70% of the forms of chronic endogenous hypercortisolism (1, 2). CD is a

Abbreviations: BMI, body mass index; CBG, cortisol-binding globulin; CD, Cushing's disease; CRT, conventional radiotherapy; CS, Cushing's syndrome; CSF, cerebrospinal fluid; DDAVP, desmopressin; DDD, dichloro-diphenyl-dichloroethane; DI, diabetes insipidus; D2R, dopamine 2 receptor; EGFR, epidermal growth factor receptor; GABA, γ-aminobutyric acid; GI, gastrointestinal; GK, Gamma Knife; HPA, hypothalamus-pituitary-adrenal; LBA, laparoscopic bilateral adrenalectomy; LDDST, low-dose dexamethasone suppression test; LINAC, linear accelerator; MLC, multileaf collimator; MRI, magnetic resonance imaging; NS, Nelson's syndrome; OBA, open bilateral adrenalectomy; OGTT, oral glucose tolerance test; PDI, permanent DI; POMC, proopiomelanocortin; PPAR, peroxisome proliferator-activated receptor; PRL, prolactin; SCRT, stereotactic conformal radiotherapy; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SMR, standardized mortality ratio; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; SSTR, somatostatin receptor; TCS, transcranial surgery; TDI, transient DI; TSS, transsphenoidal surgery.

serious endocrine disease caused by excessive secretion of cortisol from the adrenal glands as a consequence of excessive ACTH secretion from a pituitary tumor (1, 2). The pituitary tumor responsible for CD is generally an adenoma, whereas a pituitary carcinoma is a very rare cause of the disease. The pituitary adenoma responsible for CD is a microadenoma in more than 90% of cases, and a macroadenoma in less than 10% of cases; microadenomas are not visible during radiological examination in up to 40% of cases, and macroadenomas may occasionally acquire an aggressive behavior, characterized by a rapid growth and invasiveness of surrounding structures (1, 2).

The prevalence of CD is estimated to be nearly 40 cases per million, whereas the incidence of CD ranges from 1.2 to 2.4 per million per year. CD is at least three times more prevalent in women than in men, and mainly occurs during the fourth to sixth decades of life (1–3).

CD is characterized by a disruption of the hypothalamus-pituitary-adrenal (HPA) axis with consequent increase in circulating serum and urinary cortisol levels and lack of cortisol circadian rhythm (1, 2). The clinical picture of CD mainly includes weight gain with central obesity, fatigue with proximal myopathy, skin thinning with purplish striae, and diffuse bruising. The clinical picture is commonly complicated by several comorbidities, mainly including systemic arterial hypertension, diabetes mellitus, dyslipidemia, osteoporosis, and depression, together with an impairment of sexual function in men; menstrual disorders, acne, and hirsutism in women; and infertility in both men and women (1, 2).

The diagnosis of CD is a real challenge because of the variability of the clinical presentation of the disease and, particularly, the lack of discriminatory symptoms and signs in patients with CD (1, 2). As a consequence, a series of hormonal tests are required for a definitive diagnosis; however, these tests have a variable sensitivity and specificity and fail to reach 100% accuracy (4–6). Therefore, efficient screening and confirmatory diagnosis are essential before considering therapy (7). Moreover, a prompt and effective treatment is crucial to prevent the development and/or worsening of the comorbidities and clinical complications responsible for the increased mortality associated with the disease (8).

The current review summarizes the available treatments for CD, describing efficacy, in terms of control on hormone secretion and tumor mass, and safety, associated with the different treatments, and detailing specific effects on the clinical picture as well as on comorbidities and clinical complications that are the most important causes of death for patients with CD. An introduction on the mortality and morbidity of CD is included to emphasize the severity of the disease and the need for a treatment. Future available treatments and experimental therapies are also described to provide the largest possible view on perspectives in the disease management. This review systematically evaluates the efficacy and safety of the different treatments, considering the available literature published until December 31, 2014.

II. Mortality and Morbidity in Cushing's Disease

CD is associated with excessive mortality, which is mainly due to cardiovascular or infectious diseases, and their organic or systemic clinical complications. The excessive mortality is usually observed in patients who do not achieve initial surgical remission, whereas those patients who do achieve an immediate surgical cure generally have a mortality rate similar to that of the normal population (9).

A. Mortality

The studies on mortality in CD have reported nonhomogeneous results. Mortality in patients with CD has been analyzed in a series of studies, which reported the standardized mortality ratio (SMR). In these studies, the SMR of the total population of patients with CD ranged from 0.98 to 9.3 (10–20), being significantly different from the normal population in six studies, where SMR ranged from 2.39 to 9.3 (10, 15–18, 20), and similar to the normal population in five studies, where SMR ranged from 0.98 to 2.67 (11–14, 19). Moreover, eight of these studies evaluated mortality in patients submitted to surgical treatment, considering separately those who had disease remission and those with persistent disease; the results of these studies demonstrated that patients with persistent disease consistently had the highest mortality (13–20), whereas the patients with disease remission after pituitary surgery had a mortality rate generally similar to that of the general population (13–15, 17, 19). This finding suggests the importance of surgical removal of the pituitary tumor and disease remission. However, in contrast with these previous studies, the persistence of an increased mortality rate in patients who achieved disease remission after pituitary surgery has been reported in three different retrospective studies conducted in the United Kingdom (16, 18, 20). In the first of these studies, the SMR of the total population of CD patients was 4.8, with patients achieving surgical cure maintaining a significantly increased mortality (SMR, 3.3). Interestingly, patients with persistent or recurrent disease displayed a dramatically increased mortality (SMR, 16) compared with the normal population (16). In a recent study, the SMR of the total population of CD patients was 3.17, with an increased mortality rate both in patients achieving surgical cure (SMR, 2.47) and

after surgery (SMR, 4.12), although these values were reported to be not significantly different from that of the normal population (18). Finally, another recent study has demonstrated a similar mortality rate between patients cured or not cured by surgery, displaying an SMR of around 10, compared with the normal population (20). It is worthwhile noting a study conducted in New Zealand that demonstrated a persistently increased mortality rate in patients harboring either a pituitary microadenoma or macroadenoma, despite long-term remission after pituitary surgery (17). In contrast to the discordant evidence of the mortality risk in patients cured by surgery, there is consistent evidence that patients with persistent disease after initial surgery have the highest mortality rate. This finding has been clearly reported in a Danish study in which patients not cured after initial surgery had a SMR of 5.06; interestingly, patients with possible CD whose disease etiology was unproven had an SMR of 11.5. The group with unproven CD included those without clear identification of a pituitary tumor, those who did not achieve remission after surgery, and those who died before a full investigation could be performed (13).

The major cause of death in patients with CD reported in the literature is represented by cardiovascular disease and consequent cardiovascular events, although infectious diseases and consequent sepsis seem to play an important role in determining or precipitating death, and suicide associated with psychiatric disorders is also described in patients with CD (8–20).

The predictive factors for mortality have not been clearly identified in patients with CD. Indeed, whereas age at disease diagnosis seems to have a clear negative role in determining premature death (10, 11, 17, 19, 20), the evidence regarding the role of gender is discordant because an increased mortality in females (10), a similar mortality in females and males (13), and an increased mortality in males (19) have each been reported. Moreover, the higher prevalence of deaths in patients during active disease, compared with patients after surgical remission in most studies suggests a pivotal role for the exposure to cortisol excess in mortality. The presence and duration of active disease have been clearly confirmed as an important predictive factor for mortality (13–16, 19). However, the role of exposure to cortisol excess, in terms of extent and duration, still needs to be clarified. The presence of comorbidities, including systemic arterial hypertension and diabetes mellitus, has been indicated as a predictive factor for mortality in different studies (10, 16, 17). Two recent studies in a large number of patients with CD have addressed the issue of the predictive factors for mortality. One study confirmed that cardiovascular disease represented male gender, age at diagnosis, disease duration, and clinical complications elevating the risk of cardiovascular disease (21). In particular, age at diagnosis, duration of exposure to cortisol excess, and preoperative plasma ACTH concentration elevated the risk of death in the total cohort of patients; on the other hand, male gender, age at the diagnosis, and depression were the main determinants for mortality in patients who achieved immediate remission after pituitary surgery or late remission after second-line treatments (21). In the second study, mortality associated with CS was demonstrated to be strongly dependent on the multisystem morbidity of CS, although mainly cardiovascular disease and infectious diseases (22).

Table 1 summarizes the results of the main studies on mortality, including the evaluation of the SMR, in CD.

It should be taken into account that geographic variability in the management of CD can induce differences in reported mortality rates. The recent MISSION (Mortality in Cushing's Syndrome: an International and Observational Study of the European Neuroendocrine Association) study collected information on nearly 5000 patients with CS from around the world and confirmed that patients with CD had an increased mortality (crude mortality rate, 4.25), mainly associated with disease activity (crude mortality rate of patients with active CD, 24.45) and mostly secondary to cardiovascular disease, often resulting in fatal cardiovascular events, and infectious diseases, especially when leading to generalized sepsis, since myocardial infarction or heart failure represents 17.5% and severe infection or sepsis represents 17.3% of the causes of death (23). A recent meta-analysis on mortality in patients with CS, including six studies that focused on patients with CD, confirmed that CD is associated with an increased mortality, documented by an estimated cumulative SMR of 1.84. Patients with persistent or recurrent disease after surgery had a strong association with an increased mortality, with an SMR of 3.73, whereas the SMR of patients with cured disease after surgery, with an SMR of 1.2, was not significantly different from that of the normal population (24). This meta-analysis, in accordance with most of the available studies, seems to suggest that surgical cure is fundamental for protecting patients with CD from a premature death. This conclusion should, however, be interpreted with caution. Although a meta-analysis has the strength of a systematic approach, with the inclusion of only those studies with a clear SMR calculated from available data, it also has the drawback of a limited number of studies that include a relatively small number of patients with a relatively short period of follow-up and few analyzable events.

In summary, the results of the studies on mortality in

Table 1. Results of the Main Studies on Mortality in CD

First Author, Year (Ref.)	Country	Patient Type (n)	Sex Ratio (F/M), n	Duration of Follow-Up as Mean ± SE or Median (Range), y	Study Design	SMR Total Population (95% CI)	SMR Cured Disease (95% CI)	SMR Persistent/ Recurrent Disease (95% CI)	Predictive Factors	Main Causes of Death
Etxabe, 1994 (10)	Spain	CD (49)	46/3	6.3 ± 0.8	Population-based study	3.8 (2.5–17.9)[a]	NA	NA	Age at diagnosis; female gender; persistence of hypertension and abnormalities of glucose metabolism	Cardiovascular disease; infectious diseases
Swearingen, 1999 (11)	United States	CD (161)	129/32	8.7 (1–20)	Retrospective single-center study	0.98 (0.44–2.2)	NA	NA	Age at diagnosis	Cardiovascular disease; stroke
Pikkarainen, 1999 (12)	Finland	CS (74), CD (43)	CS 64/10 CD 38/5	7.4 (0–15)	Retrospective single-center study	2.67 (0.89–5.25)	NA	NA	NA	Coronary heart disease; mitral valve insufficiency and heart failure; acute myocardial infarction; pancreatitis
Lindholm, 2001 (13)	Denmark	CS (166), CD (73)[b]	CD 50/23[b]	8.1 (3.1–14.0)	National registry study	1.7 (0.68–3.5)	0.31 (0.01–1.72)	5.06 (1.86–11.0)[a]	Disease persistence	Stroke; malignancy; sepsis; rupture of aortic aneurysm[b]
Hammer, 2004 (14)	United States	CD (289)	239/50	11.1 (0.6–24.1)	Retrospective single-center study	1.42 (0.95–2.1)	1.18 (0.7–1.9)	2.8 (1.35–5.9)[a]	Disease persistence	Myocardial infarction and/or cardiac failure; cardiac arrest[c]
Dekkers, 2007 (15)	The Netherlands	CD (74)	56/18	12.8 ± 7.3	Retrospective single-center study	2.39 (1.22–3.9)[a]	1.8 (0.71–3.37)	4.38 (1.38–9.07)[a]	Disease duration	Cardiovascular disease; malignancy; infectious diseases
Clayton, 2011 (16)	United Kingdom	CD (60)	51/9	15 (0.5–41)	Retrospective single-center study	4.8 (2.8–8.3)[a]	3.3 (1.7–6.7)[a]	16 (6.7–38.4)[a]	Disease persistence; hypertension; diabetes	Cardiovascular disease; cerebrovascular disease; malignancy; rupture of aortic aneurysm
Bolland, 2011 (17)	New Zealand	CS (253), CD (188)	CS 192/61 CD 142/46	Macro, 6.9 (0–30); micro, 7.5 (0–46)	Nationwide retrospective survey	Macro, 3.5 (1.3–7.8)[a]; micro, 3.2 (2.0–4.8)[a]	Macro, 2.3 (0.4–7.5); micro, 3.1 (1.8–4.9)[a]	Macro, 5.7 (1.4–15.4)[a]; micro, 2.4 (0.4–7.8)[a]	Age at diagnosis; diabetes mellitus at last follow-up; treatment with pituitary surgery or bilateral adrenalectomy	Malignancy; ischemic heart disease; stroke; sepsis; pulmunary embolism[d]
Hassan-Smith, 2012 (18)	United Kingdom	CD (80)	63/17	10.9 (4.9–15.6)	Retrospective single-center study	3.17 (1.7–5.43)[a]	2.47 (0.8–5.77)[a]	4.12 (1.12–10.54)	NA	Cardiovascular disease; malignancy; infectious diseases
Yaneva, 2013 (19)	Bulgaria	CS (386), CD (240)	CS 324/62, CD 197/43	8.8 (0–41.2)	Retrospective single-center study	1.88 (0.69–4.08)	1.67 (0.61–3.62)[e]	2.4 (0.87–8.19)[a,f]	Age at diagnosis; male gender; disease duration; disease activity	Cardiovascular disease; cerebrovascular disease; infectious diseases and sepsis
Ntali, 2013 (20)	United Kingdom	CS (209), CD (182)	CS 157/52, CD 137/45	12 (0.1–46)	Retrospective multicenter study	9.3 (6.2–13.4)[a]	8.3 (5.1–12.7)[a]	9.9 (3.6–21.9)[a]	Age at diagnosis	Cardiovascular disease; infectious diseases and sepsis; malignancy

This table includes studies including the calculation of SMR. Abbreviations: CI, confidence interval; F, female; M, male; NA, not available.

[a] The SMR is significantly different from the general population.

[b] The population of CD considered was that with proven pituitary etiology.

[c] The main causes of death described in this study are exclusively related to the short-term follow-up (within six months after surgery), whereas information on causes of death after long-term follow-up is not available.

[d] The main causes of death are related to the entire population of patients with CS.

[e] The SMR is related to the entire population of CS.

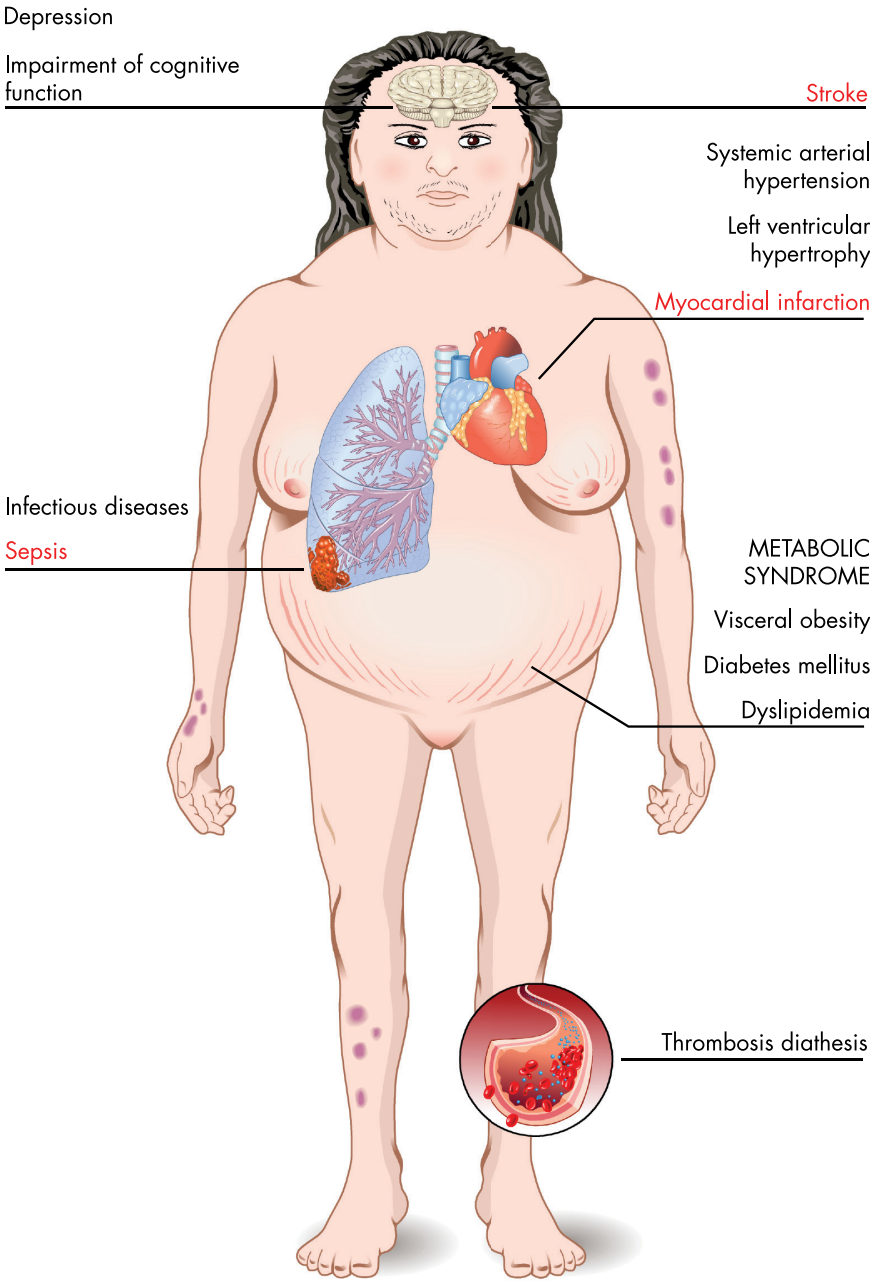
those with persistent or recurrent disease after surgery, have a seriously increased mortality, whereas some discrepancies are evident regarding the data on patients who achieved surgical cure. It cannot be excluded that these discrepancies may partially depend on the definition of "cure" applied in the single studies, considering that a consensus has never been reached on this issue. Nonetheless, it is clear that the normalization of cortisol secretion improves mortality, most likely because of the positive effects on the clinical comorbidities associated with CD, including cardiovascular disease, metabolic syndrome, infectious diseases, and neuropsychiatric disorders, which affect quality of life and represent the important risk of death for patients with CD (8).

Figure 1 shows the main comorbidities and clinical complications associated with mortality in patients with CD.

B. Cardiovascular disease

Cardiovascular disease represents the direst complication and the leading cause of death in patients with CD (8).

Figure 1.



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