Medical Management of Persistent and Recurrent Cushing Disease

Maria Fleseriu, MD[a,b,*]

KEYWORDS

• Cushing disease • Failed transphenoidal surgery • Recurrent Cushing disease
• Somatostatin receptor ligands • Pasireotide • Glucocorticoid receptor antagonist • Mifepristone
• Adrenal steroidogenesis inhibitors

KEY POINTS

- The prevalence of Cushing disease seems to be higher than previously thought.
- Morbidity and mortality are significantly increased in untreated hypercortisolemia.
- Transphenoidal surgery, in the hands of experienced neurosurgeons, is currently considered the first-line treatment of choice.
- A significant number of patients with Cushing disease could require additional medical treatment at some point in their disease course (either after failed pituitary surgery or after disease recurrence, which can be seen as late as 20 years after initial treatment).
- New therapeutic agents, such as pasireotide (a multiligand somatostatin receptor ligand that targets the corticotroph adenoma itself) and mifepristone (a glucocorticoid receptor antagonist), have recently been approved in Europe (pasireotide for treatment of Cushing disease) and the United States (mifepristone for treatment of hyperglycemia associated with Cushing syndrome).
- Individualized, multidisciplinary management to normalize devastating disease effects of hypercortisolemia is required.

INTRODUCTION

Cushing syndrome (CS) is a severe clinical state produced by prolonged and inappropriate exposure to endogenous or exogenous cortisol. The exogenous cause is usually identifiable; in contrast, diagnosis of excessive pituitary adrenocorticotropic hormone (ACTH) secretion sometimes is more complicated, especially in the early disease phase. The true incidence and prevalence of CS is difficult to estimate because of the rarity of the disorder, its insidious onset. Diagnosis is also complicated by nonspecificity and high prevalence of clinical symptoms in the general population. Furthermore, the diagnostic work-up of suspected CS requires a variety of combined biochemical tests, which often have inadequate sensitivity and specificity. Early data suggested a prevalence of 0.7 to 2.4 per million.[1] However, several recent studies have suggested

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[a] Department of Medicine, Oregon Health & Science University, 3181 Southwest Sam Jackson Park Road (BTE 472), Portland, OR 97239, USA; [b] Department of Neurological Surgery, Oregon Health & Science University, 3181 Southwest Sam Jackson Park Road (BTE 472), Portland, OR 97239, USA
* Northwest Pituitary Center, Oregon Health & Science University, 3181 Southwest Sam Jackson Park Road (BTE 472), Portland, OR 97239.
E-mail address: fleseriu@ohsu.edu

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a much higher prevalence for Cushing disease (CD) and CS.[2,3]

Moreover, epidemiologic studies in Belgium and England have revealed that the prevalence of clinically relevant pituitary tumors is 3.5- to 5-fold higher than previously estimated with an incidence rate of approximately 76 to 100 per million.[4,5] ACTH-secreting adenomas represent approximately 10% to 15% of all pituitary tumors; therefore, CD rates could be substantially higher than previously estimated.[1,6] Additionally, screening for CS in certain patient populations has revealed a prevalence of up to 3% to 11% in patients with diabetes, obesity, and osteoporosis.[7–9]

The most common etiology (70%–80%) of CS is CD, caused by an ACTH-secreting pituitary adenoma. Women are affected more than men (5:1), with peak incidence at 25 to 40 years of age.

MORBIDITY AND MORTALITY

CS is associated with increased cardiovascular morbidity and mortality. Chronic hypercortisolemia is responsible for a higher incidence of hypertension, glucose intolerance, diabetes mellitus, central obesity, hyperlipidemia, and hypercoagulability.[10] Recent evidence also suggests that increased cardiovascular risk may persist even after long-term CS remission.[11–16]

In a 2011 study, Clayton and colleagues[17] calculated standardized mortality ratio for a group of their own patients; persistent CD (adjusted for age and gender) versus CD in remission was 10.7 versus 3.3, respectively. Standardized mortality ratio data for six other studies they reviewed were 5.5 versus 1.2 in persistent CD versus CD in remission. Hypertension and diabetes mellitus were risk factors of worse outcome, as well as disease persistence and older age at diagnosis.[17] In another review of three larger studies,[18] patients with persistent CD experienced a marked increase in mortality rate compared with those experiencing initial cure (mortality rate of 3.25).

These results suggest that in patients with persistent CD early and aggressive intervention to prevent excessive mortality is required.

TREATMENT

Successful Management

For as long as CS has been described, the syndrome has presented a challenge to physicians and patients alike. Treatment goals for CD include the reversal of clinical features, the normalization of cortisol levels with minimal morbidity while preserving pituitary function, and long-term disease control without recurrence.[19] In a small number of patients with macroadenomas, removal of the tumor mass represents an additional treatment goal.

First-line therapy in most cases is transphenoidal surgery (TSS), but even in the hands of the most experienced neurosurgeon, cure rates can range from 65% to 90% for microadenomas (with even lower percentage cure rates for macroadenomas). Unfortunately, cure rates have been noted to drop further with longer follow-up.[20,21] The outcomes of TSS for CD have recently been reviewed in detail.[22,23] An accurate measurement of real outcome data is hampered by different definitions of cure or interval assessments in various studies.[24] For example, postoperative patients could be considered as in complete remission or cured, remission with relapse, or not cured with persistent hypercortisolism.[25,26]

Furthermore, even for patients who are “cured,” the risk of relapse over time is relatively high with long-term follow-up.[14,27,28] Thus, a diagnosis of remission rather than “cured” is preferable. Unfortunately, there is no ideal predictor of what could be considered permanent remission. Postoperative adrenal insufficiency has been shown to be less reliable than initially thought.[6] Conversely, a normal or slightly high postoperative cortisol level is not an absolute indicator of not being in remission. A recent multicenter study showed that 5.6% of patients, who had an initial normal or slightly high urine free cortisol (UFC) level, developed a delayed and persistent cortisol decrease after an average of 1 month postoperatively.[14] An immediate postoperative cortisol level, especially if high, could be important for a decision regarding early repeat surgery.[6,14,29]

If first-line surgery is unsuccessful, the next treatment step is presently somewhat dependent on the patient or treatment center preference. In all cases of persistent or recurrent CD, successful treatment requires close collaboration between endocrinologists, neurosurgeons, radiation oncologists, and general surgeons (**Fig. 1**).

Screening tests and localization tests are fraught with false-positives and negative results. If a patient fails surgery (unless pathology is positive for ACTH-secreting adenoma), a diagnosis reconfirmation is recommended[6] before any further treatment decision can be made.

Medical Treatment

Recently, medical treatment has played a more important role in controlling cortisol excess and its devastating physiologic effects.[21,30] Results of two large phase III prospective trials conducted over the last few years have been published that