Cushing Disease Is Not Necessarily a Progressive and Fatal Disease

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Abstract: Patients with Cushing disease are thought to have progressive and unremitting symptoms if left untreated. We report a patient with documented Cushing disease that was untreated for 26 years. A 50-year-old woman presented with a medical history consistent with longstanding Cushing syndrome. A dexamethasone suppression test done 26 years before our evaluation confirmed Cushing syndrome. She was lost to follow up and remained untreated over a 26-year span. During this period, she had episodes of fatigue, weight gain, menstrual irregularity, and hypertension. These episodes were punctuated with periods of transient cessation of her symptoms. She presented to us after worsening of symptoms. Cushing syndrome was suspected and confirmed by elevated urinary-free cortisol and 17-hydroxycorticosteroid. Pituitary magnetic resonance imaging revealed a 4-mm adenoma. A pituitary tumor was identified at transphenoidal surgery, and the patient became hypocortisolemic postoperatively. Cushing disease has generally been thought to be a progressive and unremitting disease. This case illustrates that, in contrast to our current thinking, Cushing disease is not necessarily a progressive disease.

Key Words: Cushing disease, episodic Cushing disease

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Endogenous overproduction of plasma corticosteroids leads to the signs and symptoms of Cushing syndrome. The etiologies of hypercortisolism include pituitary-dependent adrenal hyperplasia (Cushing disease), adrenal tumor, or a nonpituitary adrenocorticotropic hormone (ACTH)-producing tumor (ectopic Cushing syndrome). The most common of these etiologies is Cushing disease.[1,2] Since it was first described, Cushing disease has been thought to be unremitting and progressive if left untreated.[3] We describe a patient with documented, untreated Cushing disease for at least 26 years, who challenges this notion of unrelenting hypercortisolism.

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CASE REPORT

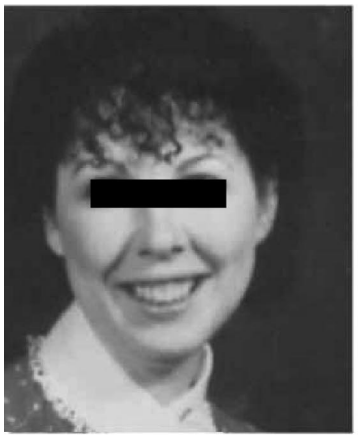
A 50-year-old white woman with a medical history of asthma, hypothyroidism, and longstanding hypertension presented with obesity (body mass index = 36 kg/m^2), severe fatigue, mild hirsutism, alopecia, scalp acne, round plethoric face, abdominal striae, bruises, buffalo hump, supraclavicular filling, and muscle atrophy. The patient was hospitalized at the age of 24 with uncontrollable hypertension refractory to medical therapy. At that time, she had the physical stigmata of Cushing syndrome, and she reported fatigue and weight gain. Her doctor performed an overnight dexamethasone test, which revealed an 8:00 AM serum cortisol of 33.7 μg/dL (normal, <5[4]). The patient was not told the test results and was lost to follow up.

Over the next 26 years, she did not seek or receive further workup or treatment and continued to have episodic fatigue, weight gain, menstrual irregularity, and hypertension. These symptoms were punctuated with episodes of transient cessation of symptoms and a general sense of well-being.

During a 3-month period in 2003, the patient had uncontrollable hypertension and weight gain. The symptoms subsided during the following 3 months and her blood pressure fell into the normal range. She lost 2 inches from her waist with no effort. This episode was followed by a return of the cushingoid symptoms, and she again sought medical care. Her new physician suspected a diagnosis of Cushing syndrome and she was referred to us for evaluation. Cushing syndrome was then confirmed by elevated urinary-free cortisol and 17-hydroxycorticosteroid excretion. Pituitary magnetic resonance imaging (MRI) revealed a 4-mm adenoma. Endoscopic pituitary surgery also identified the adenoma. The pathology specimen showed "corticotrope" hyperplasia and cortisol levels fell to the low-normal range postoperatively. Facial photographs over 26 years are shown in Figure 1.

DISCUSSION

Plotz et al described the natural history of Cushing syndrome in 1952.[3] Cushing syndrome was thought to have a 5-year mortality rate of approximately 50%. Patients with hypercortisolism died primarily from infection, cardiovascular disease, and stroke. The treatment options were rudimentary and patients suffered equally from diagnostic and therapeutic complications and progression of the disease. In many cases, the poor outcome did not reflect untreated disease, but rather the complications associated with therapy.[3] This mortality has improved as better therapeutic options become available.



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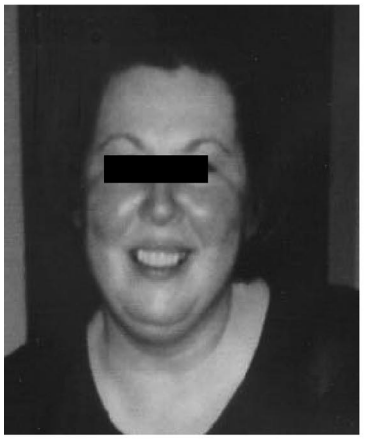

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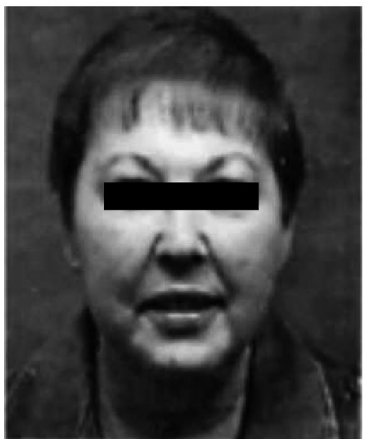

Year of Photo: 2000

FIGURE 1. Patient photos over 26 years. A, 1983; B, 1996; C, 2000.

The notion that, if left untreated, death from Cushing syndrome will occur "sooner rather than latter" has endured.

We suspect that, in some patients with Cushing disease, especially those with episodic Cushing disease, the natural history is not as bad as previously thought. Our case report illustrates this point. Some pituitary adenomas are strongly periodic with hypersecretion of ACTH interspersed with near-normal function.[5] This seems to allow the patient to recover from symptoms of Cushing syndrome during hypocortisolemic periods.

Case reports over the years show that some patients with hypercortisolism exhibited episodicity in their symptoms.[5,6] Our patient also exhibited this episodicity. Episodic hormone secretion may also explain why persons who appear cushingoid have seemingly normal biochemical studies that do not confirm the presence of the disease. Testing in a "quiescent" period when ACTH secretion and cortisol secretion are normal may lead to misleading conclusions regarding the diagnosis. Testing for Cushing syndrome should be performed during an active period to detect hypercortisolism. Multiple tests may be required.[5,6]

This case describes the natural history of a patient with episodic Cushing syndrome. This history tends to contradict the view held by many physicians that "if you had Cushing syndrome for this long, you would have been dead."

It is unlikely that the prognosis of untreated Cushing disease will ever be known. Identified disease ethically warrants intervention. All of the studies available examining the "natural history" of Cushing syndrome describe series of patients in whom most were treated or interventions were implemented.[2,3,7,8] Episodic Cushing syndrome may encompass a larger segment of the disease than currently thought and may spare the untreated patient from increased morbidity. Nevertheless, this patient had poor quality of life for most of her adult years, which could have been prevented by earlier diagnosis and treatment.

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