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Cushing's Syndrome

Series Editors:

Paul R. Conlin, MD

*Assistant Professor of Medicine, Harvard Medical School,
Director, Endocrinology, Diabetes and Metabolism Training Program,
Brigham and Women's Hospital, Boston, MA*

Bryan McIver, MB, PhD

*Consultant in Endocrinology, Mayo Clinic and Foundation,
Rochester, MN*

Contributors:

Erik K. Alexander, MD

*Instructor in Medicine, Harvard Medical School, Division of
Endocrinology, Diabetes and Hypertension, Brigham and Women's
Hospital, Boston, MA*

Robert G. Dluhy, MD

*Professor of Medicine, Harvard Medical School, Division of
Endocrinology, Diabetes and Hypertension, Brigham and Women's
Hospital, Boston, MA*

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Cushing's Syndrome

Erik K. Alexander, MD, and Robert G. Dluhy, MD

INTRODUCTION

In 1932, Harvey W. Cushing described a syndrome resulting from long-term exposure to excessive glucocorticoids.¹ Today, Cushing's syndrome is known to be a disorder of cortisol excess that has several potential causes, both endogenous and exogenous. In most cases, the endogenous causes are categorized as being either dependent or independent of adrenocorticotropic hormone (ACTH) [Table 1]. Categorizing potential etiologies of Cushing's syndrome is based on demonstrating autonomous cortisol production and then measuring serum ACTH concentrations.

ACTH-dependent etiologies, such as primary pituitary ACTH hypersecretion (termed *Cushing's disease*) by a pituitary adenoma or ectopic ACTH production, are most common and cause continuous hypersecretion of cortisol and adrenal androgens due to unregulated ACTH stimulation. Despite elevated serum cortisol concentrations, serum ACTH values are inappropriately normal or elevated, as the neoplastic cells (from a pituitary adenoma or another, nonendocrine tumor) fail to exhibit the normal negative feedback inhibition of ACTH secretion. ACTH-independent causes result from the hypersecretion of cortisol by neoplasms or from abnormal regulation of the adrenal cortex. In this setting, there is chronic suppression of anterior pituitary ACTH secretion, frequently with atrophy of the cortisol- and androgen-producing zones of the contralateral adrenal cortex.

The prevalence of endogenous Cushing's syndrome has been estimated to be about 10 cases per million, although in subgroups of obese individuals the prevalence may be greater. This figure would be considerably larger if it included the most common cause of hypercortisolism—oral ingestion of prescribed glucocorticoids for the treatment of various nonendocrine illnesses. Cushing's syndrome also may be caused by exogenous administration of glucocorticoids via topical, injected, or inhaled routes, although clinical features of Cushing's syndrome are generally mild.^{2,3} Thus, when there is clinical suspicion of an excessive glucocorticoid state, a detailed history and review of current medications is essential.

The diagnosis of Cushing's syndrome may be obvious in severe cases, but can be challenging when the degree of excess cortisol is mild.⁴ On initial examination, differentiating patients with Cushing's syndrome from the large number of patients with Cushing's syndrome phenotype is often difficult. Furthermore, several conditions can cause abnormal elevations of serum, urinary, or salivary cortisol and therefore biochemically mimic Cushing's syndrome. This disorder has been termed *pseudo-Cushing's syndrome*.

When evaluating patients suspected of having Cushing's syndrome, it is important first to document autonomous hypercortisolism, then to determine whether the excess cortisol is ACTH-dependent or ACTH-independent, and finally to ascertain the source of abnormal ACTH or cortisol overproduction. Strict adherence to structured testing in this order is important to avoid misleading information and to effectively guide further evaluation and treatment decisions. Clinicians should develop a strategy that yields the most accurate information with the least cost and inconvenience to the patient. With appropriate diagnosis and treatment, it is possible to resolve most symptoms of Cushing's syndrome, making a potentially fatal illness often curable.

ACTH-DEPENDENT CUSHING'S SYNDROME

CASE 1

Initial Presentation

A 27-year-old man is referred to an endocrinologist for evaluation of weight gain, hypertension, and proximal muscle weakness.

History

The patient was in good health until 18 months ago, when he noted a gradual change in his normal level of energy. Although he had always been athletic, he found it more difficult to exercise because of fatigue and muscle weakness. He noticed that he began to gain weight, which was apparent when he compared his appearance to that in prior photographs. On a visit