Subclinical Cushing Syndrome: A Review

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KEYWORDS

- Subclinical Cushing syndrome • Adrenal incidentalomas
- Dexamethasone-suppressive testing • Corticotropin

KEY POINTS

- Subclinical Cushing syndrome (SCS) may not be as clinically insignificant as previously postulated.
- Diagnosis of the syndrome is somewhat difficult, but possible.
- As most patients present with adrenal incidentalomas, a thorough biochemical workup by both a dedicated endocrinologist and endocrine surgeon is necessary for optimal outcome.
- Given the low rate of complications, minimally invasive adrenalectomy is recommended for patients with biochemically proven or suspected SCS who are appropriate surgical candidates.

INTRODUCTION

Subclinical Cushing syndrome (SCS) has recently become a topic of controversy and interest. The reasons for this are multifactorial. Adrenal masses known as incidentalomas, identified by radiographic imaging obtained for unrelated reasons, are detected more frequently, especially within our aging population; this is due to a combination of more refined diagnostic imaging technologies with higher resolution, and because cross-sectional imaging is much more widely used. This increase in the number of patients with adrenal masses undergoing biochemical evaluation has led to identification of patients with biochemical abnormalities without florid clinical symptoms. A unique situation has thus arisen for clinical intervention, as those patients without florid Cushing syndrome can be spared the development of significant physiologic derangements by early intervention and surgical resection. However, only a portion of patients with SCS progress to Cushing syndrome.

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Classic Cushing syndrome is characterized by the signs of hypercortisolism: moon face, buffalo hump, central obesity, easy bruising, proximal muscle wasting, deep purple striae, acne, hirsutism, and glucose intolerance. The syndrome is rare with an overall yearly incidence of 1 in 50,000.[1] Primary adrenal lesions only account for roughly 15% of the cases of Cushing syndrome. About 50% of these lesions are adenomas, with the remaining 50% stemming from functional adrenal cortical carcinomas. Nevertheless, most studies report a prevalence of 5% to 24% for SCS in patients with an adrenal incidentaloma (AI). This broad range can likely be attributed to the differing results in the diagnostic criteria used over time.[2–7]

The concept of SCS was first identified and described in 1973 by Beierwaltes and colleagues[8] and then again in 1981 by Charbonnel and colleagues.[9] SCS was defined as an increase in the overall endogenous secretion of glucocorticoids without clinical manifestations of clinical Cushing syndrome. The overwhelming consensus is that the diagnosis can be made when there is a combination of 2 distinct findings: no overt clinical signs of Cushing syndrome and at least 2 distinct alterations in the hypothalamic-pituitary-adrenal (HPA) axis. Nonetheless, patients with SCS usually have an increased prevalence of obesity, hypertension, and type 2 diabetes. It is imperative to assess all patients with an AI for biochemical production before surgical resection, as the unopposed overproduction of glucocorticoids in this case can suppress the contralateral adrenal gland and lead to postoperative Addisonian crisis, which can be fatal.[10]

DEFINITION

SCS presents in patients with a clinically nonfunctioning adrenal adenoma, likely identified for an unrelated reason on diagnostic imaging. Before the term SCS took hold, the term preclinical Cushing syndrome was used and is still used interchangeably. However, this terminology is misleading because the overwhelming majority of patients with SCS will not progress to clinically apparent Cushing syndrome, as the term implies. Therefore, the terminology of SCS has become the preferred and more accurate modality of description.[1]

To facilitate the definition of the disease, a National Institutes of Health (NIH) State of Science Conference was convened and a better, more easily identifiable term was chosen: subclinical autonomous glucocorticoid hypersecretion.[11] The final consensus was that to concretely make the diagnosis, 2 distinct criteria must be fulfilled. First, the patient must not present with a clear Cushing syndrome phenotype, and none of the physical stigmata of the disease must be present. It is imperative that an experienced clinician examine the patient to be absolutely certain that there is no evidence of classic Cushing syndrome.[7] Second, the patient must have presented with an adrenal mass that was identified in an incidental fashion, meaning that the radiographic imaging was obtained for another reason and this lesion was subsequently identified. The likely culprit of this cortisol hypersecretion is commonly a cortical adenoma, although adrenocortical carcinoma (ACC) must not be overlooked[12,13]; however, given the natural course of ACC one must question whether the terminology of SCS can truly apply.[14]

DIAGNOSIS

Rationale

Diagnosis of hypercortisolism may be laborious, even in cases of overt disease. Because of the subtle nature of the clinical manifestations of SCS as already described, biochemical tests are crucial in establishing a diagnosis. Several additional