

Editorial

Cyclic Cushing syndrome: definitions and treatment implications

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The authors review the literature regarding the definition, clinical features, origin, pathophysiology, and diagnosis of cyclic Cushing syndrome (CS). They suggest that it is increasingly recognized as a clinical entity.

Periodic hormonogenesis due to endocrine tumors and variable hormone secretion, including hypersecretion, in healthy individuals is known to occur. The medical literature contains well-documented cases of a few patients with episodic hypersecretion of cortisol. One limitation of these reports is that many of the patients underwent investigation when precise methods of measuring cortisol production were not available. Earlier and imprecise methods of assessing cortisol production included 24-hour urine 17 hydroxysteroid and urinary free cortisol by radioimmunoassay. Currently, the most precise method of measuring 24-hour urinary free cortisol is by tandem mass spectrometry, not by high-performance liquid chromatography as recommended by the authors.

Regarding the origin of cyclic CS, the authors comment that adrenocorticotrophic hormone (ACTH) staining and Crooke hyaline changes may be negative in tumor tissue because of the absence of persistently elevated blood ACTH and cortisol levels. The diagnosis of a pituitary adenoma requires loss of normal acinar architecture as shown by the reticulin stain and positive immunostaining of ACTH-producing cells in the adenoma. Because Crooke hyaline change reflects elevated cortisol levels of any origin, this is nonspecific and, as the authors note, may not be present in cyclic CS.

The most precise method of diagnosing a pituitary cause is the inferior petrosal sinus sampling study. Limitations, however, exist. It cannot be used to diagnose CS because healthy volunteers have the same central-to-peripheral ACTH gradient as patients with pituitary-dependent CS (that is, a “positive” study). A “negative” study (no central-to-peripheral gradient) in the presence of a pituitary adeno-

ma may occur because of aberrant venous drainage from the pituitary, as has been previously reported.

The authors state that a diagnosis of cyclic CS should be considered in patients in whom cushingoid features are slow to resolve or in whom there is a return of signs and symptoms after uncomplicated operative interventions. The more likely explanation for slow resolution of cushingoid features is that the process often takes 6 to 12 months, particularly in patients with long-standing disease. Regarding individuals in whom signs and symptoms have returned after surgery, recurrent disease due to the remaining ACTH-producing adenoma cells is more probable, because a second and more extensive operation may result in remission.

A topic not addressed is that many patients who are obese, depressed, hypertensive, or diabetic have “researched” the Internet and are convinced they have CS. When multiple diagnostic studies fail to confirm hypercortisolism, the query is invariably the possibility of cyclic CS. As demonstrated in this review, the cyclic CS is rare and with precise hormone measurements, it should be easier to diagnose this uncommon condition.

RESPONSE: We thank Dr. Vance for her insightful editorial. As noted, cyclical CS is a complex entity and can be easily overdiagnosed in the patient with coincidentally associated nonspecific signs and symptoms of CS. However, it can also be underdiagnosed in the patient with variable ACTH release from a tumor. Careful assessment of history, physical, and biochemical evidence of hypercortisolemia should result in correct differentiation of cyclic CS from pseudo-CS in most cases.

As noted by Dr. Vance, precise measurement of hypercortisolemia is a critical aspect of correctly identifying patients with CS, including identifying those with the variable cortisol overproduction seen in cyclical CS. Assess-

ment of urinary free cortisol in a 24-hour collection is a common and reliable means of identifying hypercortisolemia because there is a marked rise in urinary cortisol level as the serum cortisol level exceeds serum cortisol-binding globulin. Historically, various radioimmunoassay methods were developed for the detection of urinary cortisol, but many laboratories have replaced these tests with more sensitive and specific chromatographic methods, including liquid chromatography with ultraviolet absorbance detection, liquid chromatography mass spectrometry, and gas chromatography mass spectrometry.^{3,4}

As noted, once ACTH-dependent CS has been carefully diagnosed, inferior petrosal sinus sampling (IPSS) can be used to localize inappropriate ACTH production from a tumor; it is a highly accurate means of differentiating ACTH production from a pituitary tumor compared with an ectopic source and has some utility in lateralizing the ACTH-producing tumor within the pituitary itself. In addition to errors caused by aberrant venous drainage, IPSS results can erroneously suggest an ectopic source of ACTH production if the test is performed at a time of diminished ACTH production due to a pituitary tumor, as can occur in cyclic CS. Therefore, IPSS is ideally performed during states of hypercortisolemia.

The postoperative course after transsphenoidal microadenectomy is complicated, and, as noted by Dr. Vance, patients can present with slow-to-resolve clinical features of hypercortisolemia despite having undergone complete resection of the pituitary tumor. However, incomplete adenectomy can also result in slow-to-resolve clinical features of hypercortisolemia and an initial normalization of 24-hour urinary free cortisol. Therefore, the identification of

persistent or recurrent CS can be difficult. When incomplete resection or recurrence of an ACTH-producing pituitary tumor occurs—because the tumor burden is typically diminished compared with the original presentation—the potential variability of ACTH production seen in nearly all CS pituitary adenomas can result in cortisol levels that dip into the normal range, yielding a variable pattern of hypercortisolemia. This may explain the apparent increases in cyclic Cushing disease detection postoperatively in some series.^{1,2}

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