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Editorial : Cyclic Cushing syndrome : a challenging diagnosis

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Abbreviation: CCS (Cyclic Cushing Syndrome), DST (Desmopressin Stimulation Test), ACTH (Adrenocorticotropic Hormone), Inferior Petrosal Sinus Sampling (BIPSS). Cushing's Syndrome (CS). Continuous Glucose Monitoring (CGM). Dexamethasone Suppression Test (DST), Late-Night Salivary Cortisol (LNSC)

Cyclic Cushing's syndrome (CCS) represents a variant of Cushing's syndrome characterized by alternating episodes of elevated cortisol levels (peaks) and spontaneous intervals of normal or reduced cortisol secretions (troughs) (1).

The widely accepted definitions of cyclic Cushing's syndrome are based on two main criteria: the first involves three peaks in cortisol levels that indicate hypercortisolemia, interspersed with two troughs reflecting euocortisolaemia. The second criterion consists of two peaks separated by one trough (1).

The duration of these phases can fluctuate, lasting anywhere from several days to 86 days or even extending over years. Cyclic Cushing's syndrome presents significant challenges within the field of modern endocrinology. It is observed more frequently in women, with a male-to-female ratio of 1:3. In comparison to those with Cushing's syndrome, patients with cyclic Cushing's syndrome tend to be older, typically between 50 and 60 years of age, and often have a history of alcohol consumption, averaging 1 to 7 drinks per week(2).

Frequently used alternative terms encompass intermittent, variable, periodic, and episodic hypercortisolism. The cyclical characteristics of this condition can complicate diagnostic processes, leading to instances of both overlooked diagnoses and incorrect diagnoses (1). If there is a suspicion of intermittent hypercortisolemia, it is advisable to conduct the procedure during the active phase of the illness. Failing to do so may lead to negative results, which could subject the patient to an unnecessary invasive procedure. Endocrinologists need to consider the potential for cyclical cortisol overproduction in all patients presenting with conflicting clinical and biochemical results. Conducting a series of tests over an initial period of 28 days can confirm or

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exclude the diagnosis in most instances (2).
The recurring pattern of this condition disrupts the effectiveness of diagnostic evaluations, leading to instances of both overlooked diagnoses and incorrect diagnoses. Individuals experiencing cyclic Cushing's syndrome may be dismissed by healthcare providers when they present during a low phase. Typically, the consideration of cyclic Cushing's syndrome emerges in patients who are suspected of having hypercortisolemia but do not fulfill the complete diagnostic criteria for any specific disorder (2).

In terms of etiology, both adrenocorticotropic hormone (ACTH)-dependent and ACTH-independent CS can manifest as CCS. Among these, Cushing's disease (CD) accounts for 54% of all etiologies and is the most common cause, ectopic ACTH syndrome accounts for 26%, and adrenal tumors account for 11%. Notably, patients with primary pigmented nodular adrenocortical disease (PPNAD) and solitary micronodular adrenocortical disease typically exhibit cyclical cortisol secretion (3).

Diagnostic tests of Cushing's syndrome is better to perform 2 out of 3 tests Test:

First is (overnight 1 mg plasma cortisol lower than 1.8 (mcg/dL) or the longer 2-day low-dose Dexamethasone suppression. Second is Late-night salivary cortisol (LNSC) (<1.5 ng/dl). Salivary cortisol is highly accurate in diagnosing CS, not good for night workers or patients with oral diseases. Third is Urinary free cortisol (lower than 85 mcg/day) (1).
Scalp hair cortisol measurement has been receiving increasing attention. Evaluating hair cortisol can be particularly beneficial for diagnosing cyclic Cushing's syndrome. Since average hair growth is approximately 1 cm per month, it enables the retrospective analysis of fluctuating cortisol levels in the bloodstream. Elevated Hair Cortisol Levels in Endogenous Hypercortisolemia. Currently, hair cortisol remains the sole method that allows for a retrospective examination of cortisol exposure over the preceding months or years, contingent on the length of the hair sample. Hair samples were collected from the occipital area and trimmed as closely to the scalp as possible. Factors such as age, sex, and alterations to the hair (like dyeing or bleaching) did not significantly impact hair cortisol concentrations; however, levels were more notably affected by psychoactive influences (4).

It can be challenging to clinically determine the cause of Cushing's syndrome (CS), particularly when imaging studies do not reveal any tumors, making the identification of a primary tumor difficult. In about 13% of individuals with CS, the primary tumor remains unidentified. The Bilateral Inferior Petrosal Sinus Sampling (BIPSS) is considered the definitive method for distinguishing Cushing's disease (CD) from ectopic adrenocorticotropic hormone (ACTH) syndrome (EAS). Following desmopressin stimulation, a central ACTH to peripheral ACTH ratio exceeding 2 is observed. Similarly, after corticotropin-releasing hormone (CRH) stimulation, a central ACTH to peripheral ACTH ratio greater than 3 is noted. These results indicate that the source of the condition is likely the pituitary gland, allowing for a diagnosis of CD. Consequently, it is essential to conduct the BIPSS test during the peak cortisol secretion in cyclic Cushing's syndrome to prevent false-negative outcomes. The BIPSS is advised when serum cortisol levels

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exceed 10 ug/dl or when the patient is experiencing hypercortisolism, which can be verified by measuring the midnight salivary cortisol level from the previous night (5).

The Desmopressin stimulation test serves as an effective diagnostic tool for Cushing's syndrome (CS) and promotes the production of ACTH and cortisol in the majority of patients with Cushing's disease (CD) In individuals without health issues, conditions such as alcoholism, depression, chronic kidney disease, poorly managed diabetes ACTH-independent CS and ectopic CS do not lead to increased levels of ACTH and cortisol. Unlike the dexamethasone suppression test (DST), the Desmopressin stimulation test remains unaffected by medications that alter dexamethasone metabolism. This test may offer distinct benefits when diagnosing Cushing's syndrome. Documenting a case where a patient with Cushing's disease had normal findings on repeat urine free cortisol (UFC), late-night salivary cortisol (LNSC plasma cortisol and DST, while the Desmopressin stimulation test consistently returned positive results. Consequently, the Desmopressin test could potentially reduce the duration required to diagnose Cushing's syndrome and facilitate prompt treatment for patients. Additionally, this approach may serve as an early indicator for monitoring the recurrence of Cushing's syndrome and function as a long-term prognostic measure to evaluate surgical outcomes. Nevertheless, due to the absence of a standardized protocol, its use is not recommended for routine diagnostics (3).

Cyclic Cushing's syndrome (CCS) is an uncommon condition marked by recurrent episodes of excess cortisol, alternating with periods of normal cortisol levels. These cycles of hypercortisolism can occur in a regular or irregular pattern, with intervals between episodes lasting anywhere from days to years. To establish a diagnosis of cyclic Cushing syndrome, it is necessary to demonstrate three peaks and two troughs in cortisol production. Literature indicates that in 54% of instances, cyclic CS is linked to a pituitary corticotroph adenoma, 26% arise from ectopic ACTH-producing tumors, and approximately 11% are associated with adrenal tumors, while the remaining cases are not classified. The underlying mechanisms of cyclic CS remain largely unclear. Most individuals with cyclic Cushing's syndrome exhibit clinical manifestations of the syndrome, which may vary in intensity or be constant, although some patients may show no clinical signs at all. The variability in symptoms and inconsistent biochemical results complicate the diagnosis of cyclic CS significantly. Regular assessments of urinary or salivary cortisol levels serve as effective and convenient screening methods for suspected cyclic CS. Once cyclic CS is biochemically validated, further imaging and laboratory evaluations depend on whether ACTH dependency is present. In cases where ectopic ACTH production is suspected, targeted biochemical assessments for carcinoid or neuroendocrine tumors are necessary, including evaluations of serotonin in platelets and/or urine, as well as measurements of chromogranin A and calcitonin(6).

Individuals diagnosed with cyclic Cushing's syndrome, marked by alternating phases of elevated cortisol levels and normal cortisol secretion, Continuous Glucose Monitoring (CGM) can serve as a simple tool to evaluate glucose levels throughout both the hypercortisolism and normocortisolism stages. The information obtained from CGM in ongoing research can uncover trends of hyperglycemia that might correlate with episodes of hypercortisolism, therefore enhancing the understanding of how variations in cortisol impact glucose metabolism.

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Management of cyclic Cushing's syndrome is almost the same lines of therapy as classic Cushing's syndrome. surgery remains the most effective and preferable method of treatment in most hormonally active adenohypophyseal masses (with prolactinoma being an exception). Unfortunately, complete resection in clinically advanced disease might not be achievable.
Surgery remains the recommended modality of treatment in cyclic Cushing's syndrome arising from ectopic ACTH-secreting tumors or hormonally active adrenal tumors (unilateral adrenalectomy) (2).
Block and replace therapy is an effective medical treatment strategy for cyclic Cushing's syndrome (CCS). This approach involves the use of steroid synthesis inhibitors alongside glucocorticoid replacement therapy. The goal is to entirely inhibit the body's production of cortisol while ensuring that adequate cortisol levels are maintained through replacement therapy. This method is particularly beneficial in CCS due to the variable nature of cortisol production (3).

Conclusion:

Cyclic Cushing's syndrome usually causes significant diagnostic problems. The diagnosis should be taken into consideration whenever clinical suspicion of hypercortisolemia meets normal results of hormonal tests.
In cyclic Cushing's syndrome, the work-up should be repeated, especially when clinical signs and symptoms reappear. Increased 24-h UFC, elevated late-night salivary and/or serum cortisol can confirm cyclic hypercortisolemia. In questionable and ambiguous cases, hair cortisol and Desmopressin stimulation test should be kept in mind as a valuable option (2).

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