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Approach to the Patient

Approach to the Patient With Cyclical Cushing Syndrome

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Abstract

Cyclical Cushing syndrome (CS) is a subentity of CS, characterized by repeated episodes of excess cortisol (peaks) followed by spontaneous periods of normal or low cortisol secretion (troughs). Although considered rare, its prevalence reaches 70 of 514 to 91 of 514 (14%-18%) in patients with CS according to its definition in some reported series and can concern all etiologies of CS. Physicians should be alert to the presence of cyclical CS in patients with fluctuating symptoms or where the results of biochemical investigations indicate eucortisolism or hypocortisolism in patients with clinical CS. Cyclicity leads to difficulties in establishing the diagnosis of CS and discovering its etiology, since patients may have paradoxical/aberrant results in biochemical investigations, including inferior petrosal sinus sampling. Similarly, cyclicity complicates the interpretation of therapeutic outcomes and interferes with medical treatments for CS. Apart from cyclicity, variability of hypercortisolism is a more common phenomenon seen in CS but can cause similar problems. Since the pathophysiology and molecular basis of cyclical CS are largely unknown, a marked variability in cortisol secretion can be considered as representing a milder aspect of cyclicity within the same continuum. In this issue of "Approach to the patient," the characteristics, main diagnostic and therapeutic pitfalls, as well as strategies for diagnosing and managing cyclicity and marked variability in CS, are discussed from the clinician's perspective using 3 clinical cases.

Key Words: Cushing syndrome, Cushing disease, cyclicity, variability, late-night salivary cortisol, steroidogenesis inhibitors

Abbreviations: ACTH, adrenocorticotropin; CD, Cushing's disease; CS, Cushing's syndrome; DST, dexamethasone suppression test; EAS, ectopic adrenocorticotropin secretion; HPA, hypothalamic-pituitary-adrenal; IPSS, inferior petrosal sinus sampling; LCS, left petrosal sinus; MRI, magnetic resonance imaging; NNH, nonneoplastic hypercortisolism; PPNAD, primary pigmented nodular adrenocortical disease; RCS, right petrosal sinus; UFC, urinary free cortisol.

Case 1

A 46-year-old woman was referred to the endocrinology department for CS. Initial clinical evaluation found facial and truncal weight gain, hirsutism, and mild specific clinical symptoms of CS, including easy bruising, fragile skin, and some purple abdominal striae. She was being treated with 2 antihypertensive drugs and had glucose intolerance. An initial biochemical evaluation was consistent with abnormal cortisol secretion of moderate intensity: 3 urinary free cortisol (UFC) measurements ranged from 1.2- to 1.4-fold the upper limit of normal range (× ULN) and midnight serum cortisol was increased, being 322 nmol/L (N < 205 nmol/L, conversion factor to µg/mL: 0.036). Chronic hypercortisolism was subsequently confirmed by the almost constantly increased, albeit highly fluctuating, late-night salivary cortisol concentrations (LNSC) at home (7 samples ranging from 10.6 to 44.0 nmol/L; N < 5.0 nmol/L). Complementary biochemical investigations were consistent with Cushing disease (CD), including nonsuppressed plasma adrenocorticotropin [ACTH] concentrations (2.8 to 4.9 pmol/L, N: 2-13 pmol/L, conversion factor to pg/mL: 4.54) and a marked response to the desmopressin test (increase in ACTH concentration from 5.3 to 14.6 pmol/L[1], expected response in CD ≥ 6.0 pmol/L[2]). As pituitary magnetic resonance imaging (MRI) was normal, inferior petrosal sinus sampling (IPSS) was scheduled 8 weeks after initial evaluation. Clinical symptoms at the time of IPSS were unchanged. Surprisingly, and despite the absence of anatomical venous variations and an adequate catheterization of the petrosal sinuses, petrosal and peripheral ACTH concentrations were low/suppressed and did not increase after desmopressin injection, while serum cortisol concentrations during the test were 320 to 350 nmol/L (Table 1). In contrast to results of previous investigations, these unexpected results suggested ACTH-independent CS; however, the adrenal computed tomography scan was normal. The patient entered a period of 3 years' follow-up observations during which several intermittent and cyclical episodes of hypercortisolism were observed (Fig. 1). The patient experienced several episodes of hypertension, which were concomitant with increases in UFC and/or LNSC, leading to the temporary introduction of new antihypertensive treatments. Conversely, she also experienced long periods (lasting 2-24 weeks) that were characterized by normal blood pressure and normal UFC and LNSC values (see Fig. 1). The duration of peaks and troughs were highly variable. Interestingly, plasma ACTH concentrations ranged between 2.3 and 10.0 pmol/L during phases of hypercortisolism and decreased to 1.4 to 7.4 pmol/L during troughs. Surprisingly, the dexamethasone suppression test results (DST – 1 mg overnight and low-dose) were always normal, irrespective of the period of sampling. Finally, after 3.5 years of follow-up, the clinical features worsened and the patient showed persistently increased UFCs (~2 ×ULN). Since pituitary MRI was still normal, a second IPSS was performed. UFC the day before IPSS was increased, being 2.1 × ULN.

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Table 1. Results of inferior petrosal sinus sampling associated with desmopressin injection in patient 1

		1st IPSS				2nd IPSS			
	Time	**0**	**2**	**5**	**15**	**0**	**2**	**5**	**15**
ACTH, pmol/L	Peripheral	0	0	1.4	1.8	2.0	5.4	13.1	18.1
	RCS	2.5	3.4	3.6	3.9	5.3	**544.6**	**604.6**	179.1
	LCS	1.5	1.5	1.6	2.2	1.9	8.4	14.7	20.6

The first IPSS was performed during a trough phase and the second IPSS 3 years later during a phase of hypercortisolism. Values in bold are maximum ACTH concentrations obtained during IPSS.
Abbreviations: ACTH, adrenocorticotropin; IPSS, inferior petrosal sinus sampling; LCS, left petrosal sinus; RCS, right petrosal sinus.

A 2.7 right baseline petrosal-to-peripheral ACTH gradient consistent with CD that increased to 100.9 at 2 minutes after desmopressin injection was observed (see Table 1). A 2-mm pituitary tumor was removed during transsphenoidal surgery and confirmed to be a corticotroph microadenoma on pathology. Morning postoperative serum cortisol levels decreased to 25 nmol/L, and the patient received hydrocortisone supplementation postoperatively. One year after surgery, hypertension and clinical features had resolved fully. The patient was still in remission after 6 years of follow-up.

Case 2

A 45-year-old woman was diagnosed with florid ACTH-dependent CS. She presented with facial and truncal obesity, skin fragility, large purple stretch marks, muscle atrophy, and had a history of type 2 diabetes and hypertension over 5 years, treated with metformin and ramipril, respectively. Initial biochemical evaluations were consistent with CD: 24-hour UFCs were 1.5 and 1.8 × ULN, serum cortisol was 75 nmol/L following a 1-mg overnight DST (N < 50 nmol/L), and plasma ACTH was unsuppressed and responded to both corticotropin-releasing hormone and desmopressin tests (1). A 10-mm left-sided pituitary corticotroph adenoma was surgically resected. Immediate postoperative serum cortisol dramatically decreased to 59 nmol/L (N: 140-540 nmol/L), and the patient was treated with hydrocortisone for 3 months until recovery from corticotropic insufficiency. Antihypertensive and glucose-lowering treatments were discontinued following pituitary surgery. Owing to the presence of a relatively large corticotroph adenoma, the short duration of postoperative corticotropic insufficiency, and the persistence of a postoperative response to the desmopressin test (2), the patient received careful follow-up to detect any recurrence of CD. Thirteen months after pituitary surgery, she described a feeling of malaise and a recurrence of the depressed mood and irritability that she had experienced during the active phase of CS. Hypertension concomitantly recurred. However, 3 UFC measurements were normal (0.8-0.9 × ULN) and borderline results were observed for the 1-mg overnight DST (serum cortisol: 48 and 55 nmol/L). As the diagnosis of recurrence could not be firmly established, a series of multiple LNSC measurements was performed over 3 months. As shown in Fig. 2, significant variability in LNSC was observed, without any obvious rhythm, including normal concentrations (<5.0 nmol/L, 8/28 samples) alternating with increased concentrations up to 17.0 nmol/L (20/28 samples). Ketoconazole was introduced at 200 mg twice a day for 6 months. The patient reported an improvement in well-being. UFC values were still normal (0.6 and 0.7 × ULN), and LNSC decreased to near normal values and with less variability (mean of 5.6 nmol/L in 3 samples, N < 5.0 nmol/L). Following 4 weeks of ketoconazole withdrawal, increased and highly variable LNSC concentrations were again observed (mean 11.0 nmol/L over 11 samples; see Fig. 2). Finally, the diagnosis of early-stage recurrence of CD was established. Due to the absence of a visible adenoma on MRI, the option of a second surgery was rejected, ketoconazole treatment was reintroduced, and pituitary radiotherapy at 45 to 50 Gy was administered. Four years later, ketoconazole treatment was able to be discontinued and the patient remained eucortisolic at the last follow-up.

Case 3

A 36-year-old woman was diagnosed with clinical CS. She complained of an 18-kg (~40-lb) increase in body weight over the last 6 years and had a plethora of large purple stretch marks. An initial biochemical evaluation showed ACTH-dependent hypercortisolism: Twenty-four–hour UFC was increased, being 4.2 and 4.7 × ULN, serum cortisol concentrations were 472 and 525 nmol/L (N < 205 nmol/L) at midnight, and 200 nmol/L following the 1-mg overnight DST (N < 50 nmol/L). Plasma ACTH was unsuppressed, being 4.0 and 5.4 pmol/L (N: 2-13 pmol/L). Pituitary MRI was normal but IPSS showed a 60.7 petrosal-to-peripheral ACTH gradient, consistent with CD. A 3-mm pituitary corticotroph microadenoma was removed via transsphenoidal surgery. Unfortunately, CS persisted postoperatively with UFC ranging from 1.8 to 2.6 × ULN. Ketoconazole was introduced (200 mg twice a day). Repeated measurements of UFC were normal (0.7-1.0 × ULN) for 6 months The patient reported a moderate improvement in clinical symptoms including weight loss of 5 kg (11 lb) and a reduction in facial erythrosis without normalization. A series of LNSC measurements were performed over 6 months. As shown in Fig. 3, LNSC fluctuated greatly between normal values (mean 1.87 nmol/L, 6/10 samples, N < 5.0 nmol/L) and unambiguous increases (up to 8.6 nmol/L in 4/10 samples) without any obvious rhythm. After discussion with the patient, and since the tolerance of ketoconazole was suboptimal, bilateral adrenalectomy was performed. The patient received hydrocortisone (20 mg/day) and fludrocortisone (100 mg/day) supplementation after surgery. Clinical symptoms (fatigue, erythrosis, sleep disorders, and irritability) rapidly resolved and she lost 14 kg (~31 lb) of weight in 1 year.

Discussion

The definition of cyclical CS is variable. While most authors define it by the occurrence of 3 peaks and 2 troughs (3, 4), others define it as only 2 peaks and 1 trough (5, 6). Various

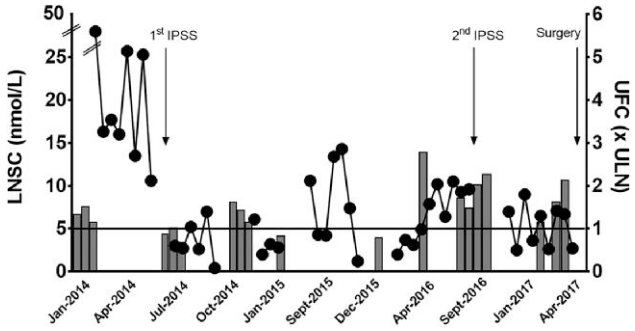

Figure 1. Case 1. Evolution of late-night salivary cortisol (LNSC; circles) and urinary free cortisol (UFC; bars) during a 3-year period showing transient periods of hypercortisolism. The horizontal line represents the upper limit of normal for UFC (expressed in × ULN) and LNSC (expressed in nmol/L). IPSS, inferior petrosal sinus sampling.

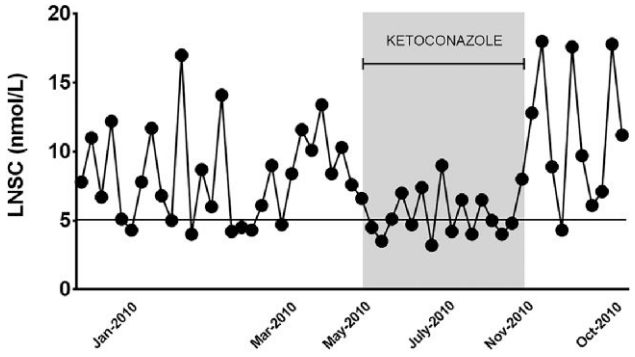

Figure 2. Case 2. Evolution of late-night salivary cortisol (LNSC; circles) during an early-stage postoperative recurrence of Cushing disease. Repeated UFC measurements were consistently normal during this period. Note the extreme variability but predominantly increased LNSC concentrations. Ketoconazole was given at 200 mg twice a day for 6 months. The horizontal black line represents the upper limit of normal for LNSC (expressed in nmol/L).

pathophysiological mechanisms have been put forward, including hypothalamic dysfunction (periodic changes in neurotransmitters such as corticotropin-releasing hormone, dopamine, or serotonin (7-10)), fluctuations in hypothalamic-pituitary-adrenal (HPA) feedback mechanisms (11-13) and/or episodic necrosis, bleeding, or infarction of the adenoma or the tumor (11, 14, 15). However, to date, the molecular mechanisms underlying the cyclical nature of cyclical CS remain uncertain and its definition is still purely descriptive. We share the conceptual view that cyclical CS represents a wide spectrum ranged along a continuum from quite unusual "true" cyclical forms, characterized by days to weeks of increased cortisol secretion, interspersed with weeks to months of biochemical eucortisolemia or hypocortisolism, to much more frequent forms of intermittent hormonogenesis, characterized by fluctuations in cortisol levels of variable intensity, from hour to hour and day to day (5, 16).

In this issue, the characteristics, main diagnostic and therapeutic pitfalls, and diagnostic and management strategies of cyclical CS are discussed based on a "classic" case (case 1). In addition, diagnostic and therapeutic issues concerning CS patients with highly variable hypercortisolism are discussed from the clinician's perspective (cases 2 and 3).

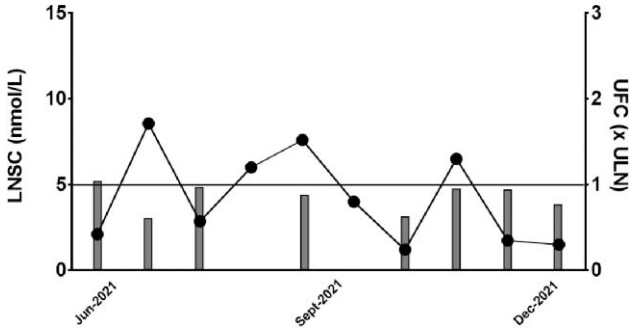

Figure 3. Case 3. Evolution of late-night salivary cortisol (LNSC; circles) and urinary free cortisol (UFC; bars) during treatment with ketoconazole (200 mg twice a day during for 6 months). Note the persistent variability of LNSC including increased levels in contrast with normal levels of 24-hour UFC. The horizontal line represents the upper limit of normal for UFC (expressed in × ULN) and LNSC (expressed in nmol/L).

Case 1: Cyclicity Interferes With the Results of Diagnostic Procedures, Often Leading to Missed Diagnoses and Misdiagnoses.

Definition, prevalence, and characteristics of cyclical Cushing syndrome

Patient 1 has a "classic" form of cyclical CS characterized by successive periods of spontaneous excessive cortisol secretion (peaks) alternating with periods of normal secretion or hypersecretion (troughs). Periods of glucocorticoid secretion fluctuated greatly in intensity and regularity, with peak duration ranging from a few hours to months, and irregular and unpredictable intervals between the peaks (see Fig. 1). This picture is similar to that seen in the majority of cases described in the literature, with an absence of any defined rhythm and periods of hypercortisolism ranging from a few hours to a few months (12 hours to 86 days, average period 21 days) (5). Peaks of hypercortisolism separated by several years (3-5 years) (15, 17-20), or peaks occurring at regular intervals (13) have been less frequently described.

Based on data from 5 selected comparative series, the prevalence of cyclicity varies according to its definition, from 14% (3 peaks and 2 troughs) to 18% (2 peaks and 1 trough) of patients with CD, and is therefore not a particularly rare phenomenon (6, 21-24).

Clinical presentations of cyclical Cushing disease

In an exhaustive review of the literature (5), the following clinical signs and their prevalence have been described in cyclical CS populations: weight gain (51%, 43%-59%), moon face (51%, 42%-60%), muscle weakness (45%, 38%-53%), bruising (35%, 28%-43%), edema (32%, 25%-40%), hirsutism (48%, 39%-57%), and menstrual irregularities (27%, 21%-37%) (5). Likewise, hypertension (60%, 53%-66%), obesity (56%, 49%-63%), diabetes (31%, 24%-38%), osteoporosis (14%, 9%-19%), depression and emotional lability (38%, 31%-45%), infections (16%, 11%-23%), insomnia (7%, 4%-12%), and thromboembolic complications (5%, 2%-10%) have been reported (5). The prevalence of these signs is roughly similar to that described in noncyclical CS (25).

Typically, symptoms appear or worsen during secretory periods and can regress completely during troughs. This type of presentation should therefore be a clue to cyclical CS.

However, similar to our patient with rapidly alternating secretory cycles, clinical symptoms may also persist between 2 periods of hypercortisolism (15, 17, 20, 22, 26-28). As the clinical expression of CS is highly variable among patients for multiple factors (duration, intensity of hypercortisolism, sex, age, and individual organ vulnerability to cortisol excess), it is important for the clinician to follow target clinical symptoms that are prominent in each individual patient to perform biochemical investigations during a secretory period. For example, blood pressure dysregulation was a sensitive marker of hypercortisolism in our patient, as hypertension recurred during peaks. Transient episodes of hyperglycemia, periodic hypokalemia, dependent edema, or changes in body weight have also been documented to identify periods of excessive cortisol secretion in patients with cyclical CD or ectopic CS (29-31).

Biochemical diagnosis of cyclical Cushing syndrome

The diagnostic strategy for cyclical CS remains similar to that for noncyclical CS. During a peak, biochemical investigations usually allow the diagnosis of CS. However, the main challenge of cyclical CS is the interpretation of the biochemical investigations during troughs.

For patient 1, the 1-mg overnight DST was particularly misleading. Indeed, throughout the diagnostic process, and even when UFC and LNSC were elevated, adequate suppression of cortisol after dexamethasone administration was found. This atypical feature, which has also been observed in noncyclical CS, supports the hypothesis of a persistent negative feedback effect of glucocorticoids on the HPA axis. Above a certain threshold, and intermittently, cortisol excess could block the secretion of pituitary ACTH and therefore block cortisol secretion. Conversely, some studies suggest that patients with cyclical and episodic CS are more likely to have paradoxical responses to dexamethasone, that is, increased cortisol secretion following dexamethasone administration (26, 31, 32), as has been observed, together with glucocorticoid receptor expression, in adrenal nodules in primary pigmented nodular adrenocortical disease (PPNAD) (33). However, spontaneous random fluctuations in cortisol secretion and a lack of a causal relationship between cortisol secretion and dexamethasone intake are alternative explanations for this phenomenon.

If cyclical CS is suspected, it is essential to repeat feasible biochemical investigations. Performing iterative 24-hour UFC measurements is cumbersome and, although the use of urinary cortisol to creatinine ratios on the first morning urine sample has been proposed for diagnosing cyclical CS (34), this strategy has not gained wide acceptance. LNSC is a noninvasive investigation that can be easily repeated at home, allowing day-to-day evaluation of cortisol secretory status in a real-life setting. In our patient, LNSC series during episodes of hypertension confirmed the occurrence of transient periods of obvious hypercortisolism. In an amazing case report (35), more than 100 consecutive salivary cortisol samples were taken from a patient living in North Africa and were sent to a central laboratory in Paris, allowing the remote diagnosis of cyclical CS. These demonstrated excessive and intermittent cortisol production prior to any treatment, allowed therapeutic efficacy to be monitored, and detected relapses. In a retrospective study (23) including 164 patients with CD, 38 of whom were cyclical, the diagnostic sensitivity of LNSC in establishing cyclical CD was 74% (28/38 patients) and was higher than that of UFC (45% [17/38 patients]).

The use of hair cortisol levels may also be useful in cases of strong suspicion of cyclical forms. Cortisol is incorporated into hair cells by diffusion from capillaries, and sweat glands in the skin generate cortisone from cortisol in hair. With hair having a growth rate of approximately 1 cm/month, hair is a suitable matrix for the estimation of mid- to long-term tissue exposure to circulating cortisol. Studies have reported a similar diagnostic performance of cortisol/cortisone measurement in a single hair sample to that of UFC in patients with overt CS (36). Owing to its ability to reflect long-term glucocorticoid exposure, hair cortisol measurement may be particularly useful for diagnosing intermittent/cyclical CS. By measuring cortisol in consecutive 1-cm hair segments, the timeline of cortisol exposure, and correspondence between the clinical and biochemical course of the disease, could be established in 6 patients with cyclical hypercortisolism (37). However, hair cortisol measurement may not be helpful in patients with very short intervals of hypercortisolism, as an entire centimeter of scalp hair is used for the assay.

Diagnosis in excess cyclical Cushing syndrome: nonneoplastic hypercortisolism ("pseudo-Cushing syndrome") and false positives of biochemical tests

Various pathological conditions, including neuropsychiatric disorders and alcoholism, can induce a functional ACTH-dependent activation of the HPA axis termed "*nonneoplastic hypercortisolism*" (NNH) (38). Its association with nonspecific clinical features of CS such as obesity, depressed mood, hypertension, and type 2 diabetes has been defined as "pseudo-Cushing syndrome." However, hypercortisolism may fluctuate due to different causes, such as intermittent alcohol abuse and alcohol withdrawal, raising the hypothesis of cyclical CS. Several papers have extensively discussed the difficulty of diagnosing NNH, with the best criterion being the disappearance of hypercortisolism with treatment or avoidance of the cause (39, 40). Based on our experience of patients referred to our tertiary health care center, we think it is worth mentioning the risk of overly considering the hypothesis of cyclical CS due to the limited performance of each of the biochemical tests used to diagnose CS (38). Indeed, the probability of false positives for biochemical investigations of the HPA axis increases with the decrease of the a priori probability of CS (41). This means that in a diabetic, obese, or hypertensive patient with no specific symptoms of CS, there is a high probability that the results of an abnormal UFC, 1-mg overnight DST, or LNSC represent false positives (41, 42). This may lead to repeated multiple endocrine investigations, resulting in nonhomogeneous and variable results for biochemical tests that reinforce the hypothesis of cyclical hypercortisolism. It is therefore important to keep in mind the importance of careful physical examinations of patients and guidelines according to which patients should be explored for CS (1, 25, 43). In addition, in patients with a low suspicion of CS, follow-up should be clinical, directed to detection of new features of CS, rather than to repetitive screening.

Difficulties in Diagnosing the Etiology of Cyclical Cushing Syndrome

Both ACTH-dependent and ACTH-independent CS can present as cyclical CS. The prevalence of etiologies in patients with cyclical CS is identical to that of CS in the general population. Accordingly, and as illustrated in our case, pituitary

adenomas (CD) account for the majority of cases (67% in a meta-analysis (5), which includes data from 212 cases from series and case reports). This may explain why most patients are women (78%), with an average age of 45 years (SD 15.5; range, 18-78 years) (5). However, ectopic secretion of ACTH by neuroendocrine tumors accounts for 17% of reported cases (5). The majority of patients with ectopic ACTH secretion (EAS) have pulmonary or thymic neuroendocrine tumors (31% and 25%, respectively) (44). In addition, in 11% of cases, cyclical SC is due to PPNAD.

Distinguishing between ACTH-dependent and ACTH-independent forms of CS can be a challenge due to the high variability of ACTH concentrations in cyclical CD, which may be inappropriate or increased during peaks, and normal or even low during troughs (3). In case 1, with histologically proven CD, the first IPPS showed suppressed peripheral and central ACTH values before and after desmopressin stimulation, which could suggest ACTH-independent CS. This phenomenon could be explained by a complete and brief "switch-off" period of adenoma activity associated with the suppression of normal pituitary corticotroph secretion by the previous period of hypercortisolism. Another hypothesis, similar to that described in silent corticotropic adenomas, would be a transient secretion of biochemically abnormal neoplastic ACTH that could not be quantified by the assay (45). Measurement of circulating ACTH values at the time of a peak in cortisol secretion is also essential to avoid misdirecting the etiological diagnosis.

In patients with ACTH-dependent hypercortisolism, IPSS is the most accurate test for differentiating CD from ectopic ACTH syndrome when pituitary MRI and body imaging are negative (1). However, an important assumption for interpreting the test is the suppression of nontumoral pituitary corticotroph secretion by cortisol excess. Incomplete suppression of the activity of normal corticotrophs in patients with EAS and intermittent/cyclical cortisol secretion may therefore result in false positives. It is therefore essential to perform IPSS during a period of hypersecretion, or ideally following a period of sustained hypercortisolism, to avoid misleading results. Several cases of misdiagnosis of IPSS performed during trough periods in cyclical CS have been reported (29, 46, 47), suggesting an EAS in patients with histologically proven cyclical CD (47) and, conversely, suggesting CD in patients with histologically proven EAS (29, 46). For example, Albani et al (29) reported a highly challenging case of a patient with cyclical EAS whose first IPSS, performed during a trough, argued for pituitary ACTH overproduction and resulted in unnecessary transsphenoidal surgery, while a second IPSS, performed during an active phase, suggested EAS. In a review of the literature, the positive and negative predictive values of IPSS, in confirming the pituitary source of ACTH secretion, decreased from 100% to 42% and from 100% to 73%, respectively, depending on it being performed during a peak or during a trough (5). As changes in cortisol secretion are unpredictable, it is essential to confirm that the patient is in an active CS phase, with at least increased UFC, LNSC, or serum cortisol just before performing IPSS (1). However, a sustained period of hypercortisolism might be necessary to ensure suppression of the normal corticotrophs.

Finally, in patients with ACTH-independent CS, cyclicity has been reported as a common feature of PPNAD and is described in up to one-quarter of patients (21, 48). Imaging results for the adrenals are generally normal in this disease, resulting in a greater diagnostic challenge.

Case 2: Cyclicity Is a Common Phenomenon and a Diagnostic Issue During Early-Stage Recurrence of Cushing Disease Following Pituitary Surgery

Pituitary surgery, performed by an expert neurosurgeon, is the first-line treatment of CD (1, 49). However, despite initial remission, CD recurs in approximately 20% of patients (1, 25, 50) and prolonged, if not life-long, follow-up is therefore recommended (1, 25). The persistence of cortisol-induced comorbidities and persistently increased mortality in patients with a history of CD appear to correlate with the duration of exposure to cortisol excess (1, 25, 51-53). Consequently, an early diagnosis of recurrence, to ensure rapid treatment, is mandatory to reduce the risk of residual morbidity. Several studies have shown that postoperative alterations in the circadian rhythm of the HPA axis are the first biochemical signs of recurrence, and precede other alterations such as impaired feedback (as evaluated by 1-mg overnight DST) and obvious cortisol excess (as evaluated by UFC) (54-57). Consequently, LNSC is currently recommended as a first-line procedure for the biochemical follow-up of operated CD patients (1, 56, 57). Although the advantages of early therapeutic intervention at a stage when hypercortisolism is not biochemically obvious are disputed (25), mild hypercortisolism, such as that seen in mild autonomous cortisol secretion adenoma, is associated with increased morbidity and mortality (58), and a benefit of treating early when UFC is still normal has been shown in a small series of CD patients with clinical symptoms of hypercortisolism (59).

However, a few studies in small cohorts have shown that cyclicity is a common phenomenon at an early stage during recurrence. Atkinson et al (60) reported 20 years ago that up to 60% of recurring patients demonstrated definite cyclical cortisol secretion for some period. Cyclicity therefore represents a major diagnostic trap for the use of LNSC as illustrated by the findings in patient 2 (see Fig. 2). Similarly to this example, in a follow-up prospective study of 8 CD patients with confirmed early recurrence, all had at least 2 normal LNSCs and, in 4 of these patients, more than 50% of LNSCs performed were normal (61). In our postoperative study of 36 patients in whom multiple LNSC were performed, the intrapatient variability in LNSC was significantly increased in the 18 patients with early-stage recurrence, compared to patients in remission, and 8 of these 18 patients had definite cyclical cortisol secretion (56). Whether this represents an intrinsic "true" cyclicity of adenomatous corticotrophs or a magnification of variable hormonogenesis at the relatively low levels of cortisol remains open to question. The potential diagnostic drawbacks of these fluctuations are absent when cortisol levels fluctuate within an obviously increased range (and therefore do not correspond to the criteria of cyclicity), contrary to the situation in patients with mild hypercortisolism, where biochemical endocrine abnormalities fluctuate around the limits of normal. This phenomenon may explain the decreased sensitivity of LNSC, irrespective of the method used, for the diagnosis of recurrence of CD, compared to that in de novo patients with clinical suspicion of CS (62, 63). In any case, owing to the large intraindividual variability in LNSCs in this period of the disease, more than 2 saliva samples, and strategies using 3 to 4 saliva samples and a

revised threshold, have been proposed to ensure an optimal diagnostic performance (56).

Case 3: Cyclicity, Variability, and Challenges for the Treatment of Cushing Syndrome

Resection of the primary lesion underlying CS is the only therapeutic option that can offer definitive cure of the disease (1, 49). As nonadenomatous corticotroph cells are suppressed by the chronic hypercortisolism, postoperative hypocortisolemia is considered to be a marker of remission, although eucortisolism is also compatible with sustained remission (1, 25). Cyclical CS with a trough phase concurrent with the time of surgery can be responsible for an erroneous diagnosis of remission and explain discordant results of suppressed cortisolemia in the immediate postoperative period and then later relapse. This situation has been described particularly in CD (5, 22). Careful and prolonged follow-up is therefore especially recommended for patients in whom cyclical CD has been diagnosed prior to surgery.

Medical treatment is one therapeutic option when surgery fails to remove the primary lesion underlying CS or when surgery is impossible. The most common use of steroidogenesis inhibitors and drugs targeting pituitary corticotroph adenomas (pasireotide and cabergoline) for CD is a titration strategy including adaptation of drug dosage to UFC, while avoiding adrenal insufficiency and drug-related side effects (64). Cortisol levels at a given time are therefore the result of 2 contradictory forces: spontaneous cortisol secretion and inhibition of this by medical treatment. Obviously, cyclical disease may render medical control extremely difficult and lead to alternating periods of overtreatment and undertreatment with a fixed drug dosage, as illustrated in some publications (6). Marked variability in cortisol secretion is more common than cyclicity and, in the absence of known pathophysiological mechanisms, may represent a mild aspect of cyclicity within a unique continuum. In a series of 152 patients with persistent/recurrent or de novo CD who were free of medication, the 95% CI of median intrapatient variability of UFC within 4 consecutive measurements reached 71%, with the widest intrapatient variability being 217 to 5081 µg/24 hours ($N < 53$ µg/24 hours) (65). Such wide random variability in UFC levels may also complicate adaptation of the drug dosage and be responsible for occasional and transient undertreatment or overtreatment using a fixed dose (66). We speculate that, once UFC is considered normalized, these episodes are likely to be ignored in real-life outpatient settings where a tight biochemical follow-up is impossible but may have detrimental consequences in the long term. The prevalence of this phenomenon is difficult to precisely assess. However, data and supplemental information issued from large randomized controlled trials conducted with various drugs suggest that transient "escapes" may affect 12% to 42% of patients (67-71). In all cases, we encourage individualization of patients with high variability in hypercortisolism prior to treatment, since this variability at the time of diagnosis is likely to persist following failure to remove the primary lesion (6). Identification of such patients should lead to an increased scrutiny for episodes of relative excess and deficits in cortisol and their clinical consequences. It is therefore important to discuss alternative therapeutic strategies among experienced medicosurgical teams when medical treatment of cyclical CS and highly variable hypercortisolism is necessary. Apart from radical treatment, such as bilateral adrenalectomy for ACTH-dependent CS, a "block-and-replace" strategy in which cortisol is reduced to minimally detectable levels and then glucocorticoid replacement is added is appropriate in this situation, ensuring control of hypercortisolism while avoiding multiple biochemical follow-up investigations and adaptations in drug dosage (49, 64, 72). It should be acknowledged that the "block-and-replace" strategy carries an additional risk of nonspecific side effects of drugs and increases the cost of treatments but the risk of adrenal insufficiency is lower than in patients treated using a titration strategy (64, 72) treated. However, it requires, similarly to addisonian patients, careful education to increase the hydrocortisone dosage when needed to prevent episodes of adrenal crisis (64, 72).

More subtle variability in cortisol secretion in patients receiving cortisol-lowering drugs may also result in imperfections in their medical treatment. In accordance with the abundant data emphasizing the physiological importance of the circadian rhythm of cortisol (73), it has been shown that CD patients treated with cortisol-lowering drugs, and with both normalized UFC and LNSC, showed a greater improvement in clinical features compared to patients with only normalized UFC and persistent increases in LNSC (74, 75). Similarly, it has been reported that definitive cure of hypercortisolism using repeat pituitary surgery, or bilateral adrenalectomy, leads to clinical improvements in patients previously considered as controlled, that is, with normal UFC levels under medical treatments (76). These data suggest that normalization of LNSC should be a biochemical target once UFC is controlled, at least for mid- to long-term treatments, to improve cortisol-related comorbidities as much as possible. However, this goal was obtained in only 17% to 44% of medically treated patients who had normalized UFC in published series (69, 70, 77). Normalizing LNSC may require administration of drugs in a "reverse circadian" fashion, that is, higher evening doses than those given in the morning. However, this strategy may induce morning hypocortisolism and requires careful measurement of morning serum or saliva cortisol. Other strategies include multiple intakes of short-acting steroidogenesis inhibitors such as metyrapone, or a combination of late afternoon/evening intake of metyrapone with other agents (64, 78). However, the variability of nocturnal cortisol secretion may be an obstacle to the goal of normalizing LNSC, as illustrated in clinical cases 2 and 3. In a prospective study using 6 late-night saliva samples drawn over a 3-month period, we found that, as a group, pharmacologically treated CD patients with constant normalized UFCs had significantly increased LNSC and LNSC variability compared to patients surgically cured of CD (74). Importantly, patients with intermittent increases in nocturnal cortisol had increased concentrations of cortisol and cortisone in hair samples, providing evidence of persistent mild hypercortisolism despite normal UFC levels during the investigation period, worse clinical scores, and an increased requirement for antihypertensive drugs (74).

This inherent variability in cortisol production therefore calls into question both the number of saliva samples required in clinical routine to assess the circadian rhythm of cortisol (61), and the feasibility of permanently normalizing evening cortisol production in all pharmacologically treated CD patients. Ultimately, this calls into question the relevance of treating patients (and more specifically CD patients) with medical treatments over extended periods.

Conclusions

Variable hormonogenesis is a common feature in CS and shows a wide spectrum of intensity. We suggest that cyclical CS is one end of this spectrum. Understanding the pathophysiology and molecular mechanisms of cyclicity may or may not confirm this hypothesis, leading to a better understanding of the behavior of endocrine-secreting tumors, and possibly giving rise to new therapeutic agents. In clinical practice, knowledge of the characteristics of "classic" cyclical CS is important to avoid the multiple pitfalls in its diagnosis and treatment. However, marked variability in CS appears to be a greater clinical challenge in everyday practice and, more specifically, a challenge for the diagnosis of early postoperative recurrence of CD and for maximizing the efficacy of pharmacological cortisol-lowering agents.

Disclosures

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Data Availability Statement

Data sharing is not applicable to this article.

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