Case Report

# Resolution of Cyclicity After Pasireotide LAR in a Patient With Cushing Disease

Márcio Carlos Machado, MD, PhD [1, 2, 3, *], Valter Angelo Sperling Cescato, MD, PhD [4], Maria Candida Barisson Villares Fragoso, MD, PhD [5], Marcello Delano Bronstein, MD, PhD [1, 2]

[1] Neuroendocrine Unit, Division of Endocrinology and Metabolism, University of Sao Paulo Medical School, Sao Paulo, SP, Brazil
[2] Laboratory of Cellular and Molecular Endocrinology/LIM25, University of Sao Paulo Medical School, Sao Paulo, SP, Brazil
[3] Endocrinology Service, AC Camargo Cancer Center, Sao Paulo, SP, Brazil
[4] Neurosurgery Service, University of Sao Paulo Medical School, Sao Paulo, SP, Brazil
[5] Adrenal Unit, Division of Endocrinology and Metabolism, University of Sao Paulo Medical School, Sao Paulo, SP, Brazil

## A R T I C L E   I N F O

## A B S T R A C T

*Objective:* The cyclicity (CIC) of cortisol spontaneously occurs in a minority of patients with Cushing syndrome (CS). When it arises, diagnostic and therapeutic approaches become more challenging. This study aimed to report a patient with Cushing disease (CD) who achieved normalization of cortisol and CIC pattern with pasireotide long-acting release (pasi/LAR).
*Methods:* A 43-year-old female patient related an 8-month history of CS. An 8-mm pituitary nodule depicted by magnetic resonance imaging, serum cortisol suppression of >50% after 8 mg of dexamethasone therapy, and the absence of other lesions were compatible with a CD diagnosis. The patient presented with a CIC pattern with 1 episode before and 17 episodes after an unsuccessful pituitary surgery.
*Results:* Medical treatment with cabergoline alone up to 3.5 mg/wk and a combined treatment with ketoconazole 400 mg/d did not improve CIC CS. Pasi/LAR was initiated at a dose of 20 mg/mo. A few days after the first dose, the patient experienced symptoms suggestive of adrenal insufficiency. The medication and dose were maintained for 24 months. During this period, there was a normalization of UFC levels and progressive clinical improvement. Additionally, new episodes of CIC were not observed.
*Conclusion:* A CD patient with a challenging issue of CIC was reported. The condition was not controlled after pituitary surgery and by the combined treatment with cabergoline and ketoconazole, although hypercortisolism was abated by the continuous use of pasi/LAR. To our knowledge, this is the first report as regards the use of this medication to control CIC in a patient with CD.
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## Introduction

The cyclicity (CIC) of cortisol secretion is a specific condition that spontaneously occurs in a minority of patients with endogenous Cushing syndrome (CS). A cycle is most commonly characterized by 2 episodes of hypercortisolism that are interposed with a phase of normalization/nadir of cortisol.[1] Its prevalence is not well established. However, 1 study that carefully analyzed the variations or cyclical patterns of cortisol secretion in a cohort of Cushing disease (CD) patients reported a prevalence of 15% before therapeutic interventions.[1]

CIC treatment is performed through the direct treatment of the etiology. However, CS remission may not be achieved even with the treatment of choice, given that surgical failure occurs in 30% to 60% of cases.[2]

The medical treatment of CIC has been previously described in case reports and mainly involves the use of drugs with action in the upper centers or in the hypothalamus.[3,4]
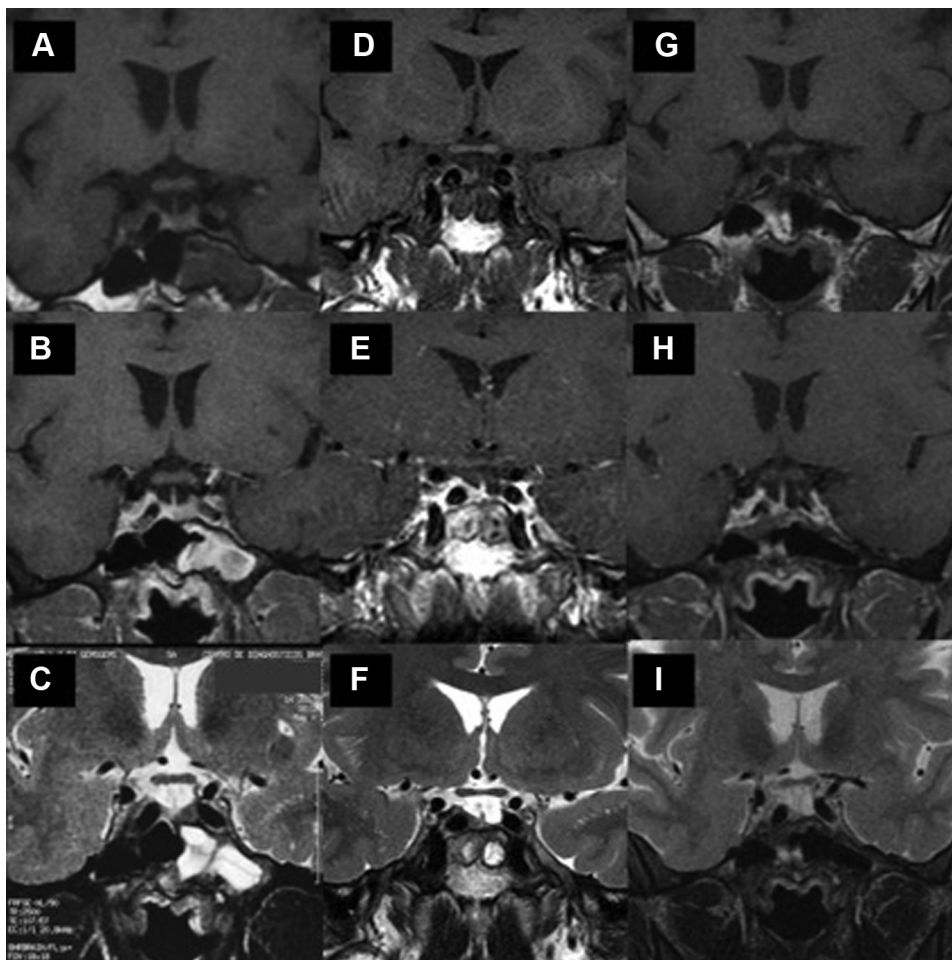
**Fig. 1.** Magnetic resonance imaging of the pituitary gland at diagnosis and evolution. *A, B,* and *C,* imaging at diagnosis (2013-2014); *D, E,* and *F,* imaging 4 months after the pituitary surgery; *G, H,* and *I*: follow-up imaging, 2019 July, 5 years postoperatively; *A, D,* and *G*: coronal T1 weighted, without gadolinium; *B, E,* and *H*: coronal T1 weighted, after gadolinium; *C, F,* and *I*: coronal T2 weighted.

Pasireotide, a new generation of somatostatin receptor ligands has been used in patients with CD[5,6] due to the predominant expression of somatostatin receptor subtype 5.[7] However, there is no description regarding the use of this medication in the particular condition of CIC.

This study aimed to report an unprecedented case of cortisol normalization in a CIC CD patient with the continuous use of pasireotide long-acting release (pasi/LAR).

## Case Report

### Diagnosis of CS and Differential Diagnosis of Adrenocorticotropic Hormone CS

A 43-year-old female was admitted to our service in July 2013. She presented with a full picture of CS, which developed in months, consisting of weight gain, central obesity, moon face and plethora, easy bruising, muscular wasting and weakness, cutaneous atrophy, headache, menstrual irregularity, depressive mood, acne, hirsutism, and osteopenia. Hormonal assessment confirmed adrenocorticotropic hormone (ACTH)–dependent CS, which a serum cortisol, after a low-dose dexamethasone suppression test of 1 mg overnight of 22.5/27.1 μg/dL (2 different days; reference [R]: <1.8 μg/dL), a late-night salivary cortisol (LNSC) of 14.5/24.7 nmol/L (2 different days; R: <1.0 nmol/L), a 24-hour urinary cortisol level (UC) of

472/455 μg/24 h (2 different days; R: <250 μg/24 h), an ACTH level of 45 pg/mL (8h00-9h00; R: <46 pg/mL), and a dehydroepiandrosterone of 641 ng/mL (R: 61-337 ng/mL). A pituitary magnetic resonance imaging (MRI) depicted an 8-mm left nodule (Fig. 1). The results of computed tomography scan of the thorax and MRI of the abdomen/pelvis were unremarkable. Serum cortisol after a high-dose dexamethasone suppression test (8 mg overnight; R: >50% of suppression) was 5.4 to 0.9 μg/dL, with 83% of suppression. At this time, the patient presented with a spontaneous clinical amelioration, weight loss, return of regular menses, improvement of muscular weakness and improvement of cutaneous thinning, LNSC of 76 ng/dL (R: <100 ng/dL), and UC of 25.1/70.0 μg/24 h (2 different days; R: 3-43 μg/24 h). Pituitary surgery was subsequently cancelled. The symptoms and hypercortisolism recurred by February 2014. The patient underwent transsphenoidal pituitary surgery by microscopic approach in June 2014, although no tumoral tissue was found in pathology evaluation. On the 10th postoperative day, serum cortisol was 23.4 μg/dL (8h00-9h00; R: 6.0-18.4 μg/dL), and ACTH was 41 pg/mL. At this point, a bilateral and simultaneous petrosal sinus sampling (BIPSS) procedure was planned, although was cancelled due to another spontaneous clinical improvement and hormonal normalization. In July 2015, after several CIC episodes, the patient underwent BIPSS with desmopressin (DDAVP; Ferring Pharmaceuticals) during a period of active hypercortisolism that was compatible to the CD diagnosis

**Table 1**
Bilateral and Simultaneous Petrosal Sinus Sampling for Diagnosis of Cushing Disease

| ACTH (pg/mL) | 0' | 3' * | 5' * | 10' * |
|---|---|---|---|---|
| Periphery | 17.4 | 19.7 | 20.1 | 35.5 |
| Right IPS | 42.0 | 401.3 | 368.6 | 65.9 |
| Left IPS | 261.3 | 502.5 | 501.8 | 1285.0 |
| CEN:PER | 15.0 | 25.5 | 24.9 | 36.2 |
| IPS:IPS | 6.2 | 1.3 | 1.4 | 19.5 |

Abbreviations: IPS = inferior petrosal sinus; CEN:PER = central to peripheral ACTH gradient; IPS:IPS = intersinus gradient.
A 24-hour urinary free cortisol in the day of the procedure (July 06, 2015): 96.6 μg/24 h (Reference: 3.0-43.0 μg/24h).
 * after desmopressin 10 μg IV

due to an intense central to peripheral ACTH gradient of 15.0 at baseline and 36.2 after peak (Table 1).

*Characteristics of CIC*

During the first 6 years of follow-up, the patient presented with clinical changes, either spontaneously or under medical treatment, and an extreme variation in cortisol levels. There were 18 well-characterized cycles (Fig. 2).

The duration and interval of the cycles were variable, ranging from few days to several months (Table 2). A larger duration (hypercortisolism phase) of cycles occurred before drug administration. After cabergoline (CAB) and ketoconazole (KTC) treatments, the cycles were shortened, although still exhibited extreme cortisol oscillations.

A parallelism of clinical improvement and normalization of hypercortisolism was observed in most but not all cycles, which is likely due to the short duration. Weight gain, worsening of arterial hypertension, edema, facial plethora, and hand tremors were the predominant clinical changes in the hypercortisolism phase. On the other hand, during the nadir phase of cortisol, the patient presented asthenia, improvement of arterial hypertension, and facial plethora. Furthermore, we performed a register of serial photographs of the patient to correlate with clinical changes during the cyclical periods; however, this strategy was not advantageous to confirm the cortisol status.

Several clinical episodes were suggestive of adrenal insufficiency (AI) as postural hypotension and dizziness, which were more frequently observed during the combined treatment of CAB and KTC, thereby suggesting a putative relationship of the last medication treatment with cortisol decrease. The patient was aware of such condition, and an oral hydrocortisone medication was prescribed if necessary.

*Treatment and Outcome*

After BIPSS and due to the absence of a visible tumor at MRI (Fig. 1 *D-F*), CAB was initiated at 1 mg/wk twice a week and was increased to the maximum dose of 3.5 mg/week (Fig. 2).

KTC was combined with CAB at a dose of 400 mg/d. A shortening of the extension of the cycles was observed during the combined treatment. However, the cycles' frequency and the extreme hormonal variations were unchanged. Additionally, the patient experienced symptoms suggestive of AI. Subsequently, KTC was suspended, and CAB was maintained at a dose of 3.5 mg/wk.

At a dose of 20 mg monthly via intramuscular injection, pasi/LAR (Signifor; Novartis) was initiated. A few days after the first dose, the patient experienced arterial hypotension, weakness, and dizziness suggestive of AI (UC, 1.9 μg/24 h; R: 3-43 μg/24 h). Oral hydrocortisone of 20 mg/d was added. Thereafter, the pasi/LAR dose was maintained for 24 months, with the last dose given in January 2021. UC normalization was observed during this period (Table 2). Additionally, new CIC episodes were not observed.

During pasi/LAR treatment, the patient exhibited a good and progressive clinical improvement, such as weight loss and humor stability, with reductions in psychiatric medications and bone mineral density improvement.

The medication was well tolerated, with just a slight increase in glucose levels (HbA1c, 5.2 ± 0.1 to 5.7 ± 0.2%, before and during pasi/LAR treatment, respectively).

This work has been performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving human subjects. An informed consent was obtained, and the Ethical and Research Committees of our institution approved this study.

**Discussion**

Among various uncertainties and challenges that involve the management of CIC is the lack of knowledge of its mechanism of action.[3] The regulation of ACTH secretion by the upper centers and hypothalamus as well as tumor apoplexy are among the suggested mechanisms.[3] A common adrenal mechanism could explain the various possible etiologies of ACTH-dependent and ACTH-independent cyclicities.

Regarding the hormonal characterization, a diagnostic difficulty exists due to the great variation in the number of cycles, intensity, and mainly the duration of the phases of CS and nadir that the patients may present, which can vary from days to years, even on an intra-individual basis.[1,8] Therefore, a serial analysis of the hormonal samples is necessary, especially with the LNSC levels due to convenience.[9,10] However, once CIC is characterized, UC samples may be more useful to guide the need for treatment. A previous study used serial samples of morning UC-to-creatinine ratio to characterize CIC.[11] The low-dose dexamethasone suppression test may present misleading results for CIC determination.[12] Finally, the measurement of hair cortisol levels was studied to retrospectively characterize CIC (~1 cm/mo), thereby allowing the creation of a cortisol status timeline.[13]

The differential diagnosis of CIC involves several situations, ranging from pseudo-Cushing states to factitious CS. We published an intriguing case in which CIC was suspected due to the extensive hormonal variations (mainly in UC levels; false positive due to the method before mass spectrometry) and due to the purposeful use of oral prednisone.[14]

Regarding etiological investigation, it should be performed during the CS phase. There are descriptions of false positives of BIPSS in patients with ectopic ACTH syndrome at the nadir of cortisol secretion. Another method that may have a questionable effectiveness is the high-dose dexamethasone suppression test, depending on the status of the cortisol level.

The treatment for CIC does not differ from the usual approach to the causative source. However, the surgical approach is often postponed due to the etiological uncertainty (eg, occult ectopic ACTH syndrome) or even due to surgical failures, which are common in CD. Therefore, bilateral adrenalectomy can be an optional treatment to resolve CS in patients with significant comorbidities.

The dopamine agonist CAB controls CS in approximately 40% of cases over the long-term period,[15] with no CIC context. In our case, there was a partial response and a reduced number of cycles, with an additional improvement after the addition of KTC. However, periods of subnormal cortisol levels were detected. Fortunately, the introduction of pasireotide has dramatically changed the patient's evolution. Pivotal studies have demonstrated a complete clinical response in approximately 30% to 50% of cases.[5,6] The patient
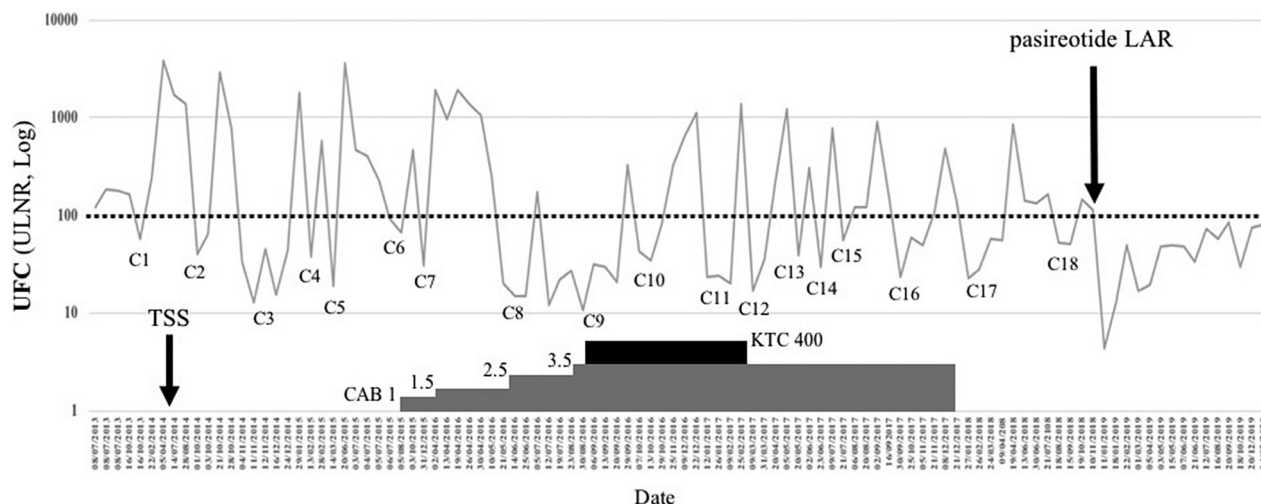
**Fig. 2.** The 24-h urinary free cortisol variations during follow-up. *CAB* = cabergoline, oral dose peer week (mg); *C* = cycle; *KTC* = ketoconazole, oral dose per day (mg); *LAR* = long-acting release; *Log* = logarithm scale; *TSS* = transsphenoidal surgery; *UFC* = urinary free cortisol, reference: 3 to 43 μg/24 h; *ULNR* = upper limit of normal range in %.

**Table 2**
Clinical and Hormonal Data From the Cyclicity of Cushing Syndrome Before and After Medications

| Parameter | No medications | Cabergoline | Cabergoline and ketoconazole | Pasireotide LAR |
|---|---|---|---|---|
| Time, months | 37 | 22 | 7 | 24 |
| LNSC, ng/dL | 380.8 ± 604.8 | 275.2 ± 306.1 | 276.9 ± 274.5 | 140.8 ± 74.4 |
|   LNSC nadir, ng/dL | 24 | 32 | 46 | 42 |
| LNSC maximum, ng/dL | 3275 | 1258 | 902 | 302 |
| UFC, μg/24 h | 305.7 ± 486.5 | 166.3 ± 238.4 | 119.2 ± 189.5 | 23.6 ± 15.0 |
|   UFC nadir, μg/24 h | 5.5 | 4.6 | 7.3 | 1.9 |
| UFC maximum, μg/24 h | 1679.0 | 840.0 | 602.4 | 53.0 |
| ACTH, pg/mL | 30.3 ± 10.7 | 25.8 ± 12.1 | 34.0 ± 12.7 | 21.3 ± 4.3 |
| Weight, kg | 76.5 ± 4.8 | 81.7 ± 1.3 | 80.4 ± 2.3 | 78.6 ± 2.3 |
| HbA1c, % | 5.5 ± 0.2 | 5.2 ± 0.1 | … | 5.7 ± 0.2 |
|   Cycles | | | | |
|   n | 8 | 6 | 4 | 0 |
|   Duration, days[*] | 137.4 ± 65.3 (30-224) | 81.5 ± 58.0 (28-180) | 72.3 ± 19.5 (54-92) | … |
|   Hypercortisolism, days (elevated UFC)[*] | 65.8 ± 64.9 (7-186) | 42.5 ± 27.6 (12-88) | 18.8 ± 19.6 (7-48) | … |
|   Nadir, days (normal UFC)[*] | 71.6 ± 37.9 (15-126) | 39.0 ± 30.8 (13-92) | 53.5 ± 17.3 (42-79) | … |

Abbreviations: ACTH = adrenocorticotropic hormone (Reference [R]: 7-63 pg/mL [8h00-9h00]); LAR = long-acting release; LNSC = late-night salivary cortisol (R: <100 ng/dL; UFC = 24-hour urinary free cortisol (R: 3-43 μg/24 h).
Parameters, mean ± standard deviation;
  [*] mean ± standard deviation and range.

exhibited an intense reduction in cortisol levels, with symptoms of AI immediately after the first injection, requiring the strategy of blocking and replacing with oral hydrocortisone. At the end of the 24-month treatment, a progressive and sustained clinical improvement was observed, a feature that did not occur even at the nadir of CIC as well as CIC resolution. The infrequent occurrence of escape that is described in CD (without CIC) with pasireotide treatment, as opposed to the 30% of cases with CAB[16] or KTC,[17] would be a theoretical advantage for our patient. Although the direct action at the corticotrophic tumor by pasireotide is known, the exact mechanism of this medication to control the CIC pattern is uncertain.

## Conclusion

We herein present a patient with CD with well-documented CIC in a challenging diagnostic and therapeutic management who demonstrated an effective clinical and laboratory response to pasireotide, with a resolution of hormonal variation. To our knowledge, this is the first case to use this medication to control CIC in a patient with CD.

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