Cyclical Cushing's Syndrome: A Diagnostic Dilemma

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Cyclical Cushing's syndrome is a rare disorder with an unknown pathophysiology. It is defined by fluctuating episodes of hypercortisolism and normal cortisol levels. Due to the variable course of the disease, diagnosing cyclical Cushing's syndrome is a common dilemma encountered in clinical practice.

A thirty-five-year-old Bahraini female presented with symptoms of exponential weight gain, hirsutism and irregular menses indicating polycystic ovarian syndrome (PCOS). The initial cortisol level was normal; however, during follow-up, lab investigations revealed fluctuating cortisol levels with prolactinemia. MRI pituitary revealed left lobe pituitary microadenoma. Various expertise input was required to achieve a diagnosis. The patient opted to seek further medical opinion in a specialized center for surgical intervention.

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Cushing's syndrome is a rare entity with an incidence of 0.7–2.4 per million populations per year. Cyclical Cushing's syndrome incidence is estimated to be 15% out of Cushing's syndrome[1,2].

Cyclical Cushing's syndrome poses a great challenge to physicians. Although it is a rare entity, Cyclical Cushing's syndrome is increasingly recognized[3]. It is a disorder with unknown pathophysiology, where a patient presents with cycles of hypercortisolism interspersed with periods of regular cortisol secretion[4]. The cycles of hypercortisolism can occur regularly or irregularly with either fluctuating or permanent signs of Cyclical Cushing's syndrome.

Studies have shown that pituitary corticotropic adenomas account for 80-90% of all non-iatrogenic adult cases of Cyclical Cushing's syndrome[5]. Adrenal tumors producing cortisol and non-pituitary adrenocorticotropic hormone (ACTH)-secreting lesions account for the remainder of cases; these include lung carcinoid, small cell lung carcinoma, pheochromocytoma, medullary thyroid carcinoma, pancreatic islet tumors and rare ovarian tumors. In addition, ectopic corticotropin-releasing hormone (CRH) producing tumors are a rare cause.

To achieve a definitive diagnosis of Cyclical Cushing's syndrome, three peaks and two troughs of cortisol production should be demonstrated. The variability of cycle lengths has been reported to be between 12 hours and 85 days[3]. Highly specific and sensitive tests are required to distinguish hypercortisolism from polycystic ovarian syndrome, depression, obesity, etc.

Due to the variability of cortisol secretion and fluctuating clinical features, Cyclical Cushing's syndrome appears to be a diagnostic dilemma many physicians encounter in clinical practice.

The aim of this presentation is to report a rare case of Cyclical Cushing's syndrome and review the different diagnostic tests and management approaches.

THE CASE

A thirty-five-year-old female with a background of hypothyroidism, diabetes mellitus, hypertension, and obesity presented with symptoms of rapid weight gain, hirsutism and irregular menses. On examination, the patient had no truncal obesity and a BMI of 48.7, the BP was 149/87. She was on levothyroxine 175 mcg, metformin hydrochloride 1 gram twice daily, spironolactone 50 mg twice daily and saxagliptin 2.5 mg daily. Laboratory investigations revealed high serum testosterone (7.26 nmol/l), low vitamin D levels (19 nmol/l) and normal serum cortisol (271 nmol/l). She was prescribed atorvastatin 20 mg tablet once daily and vitamin D capsules 50,000 iu once per week.

During follow-up, the patient presented with a few months history of neck swelling accompanied by dysphagia. Fine needle aspiration cytology revealed a benign lesion; however, due to dynamic airway compromise, a total thyroidectomy was performed. Histopathology revealed a follicular adenoma in the right lobe and papillary microcarcinoma in the left lobe.

Urinary free cortisol was sent twice, a year apart, which was within normal range (72 nmol/24 hours and 108 nmol/24 hours). During the three-year period, levels of serum cortisol varied from normal to the upper limit of normal, see figure 1. Both 48 hours and high dose dexamethasone suppression tests resulted in non-suppressible cortisol levels (390 nmol/l and 414 nmol/l, respectively). Plasma renin, aldosterone ratio, dehydroepiandrosterone (DHEA), urinary free catecholamines, urinary free metanephrines were normal.

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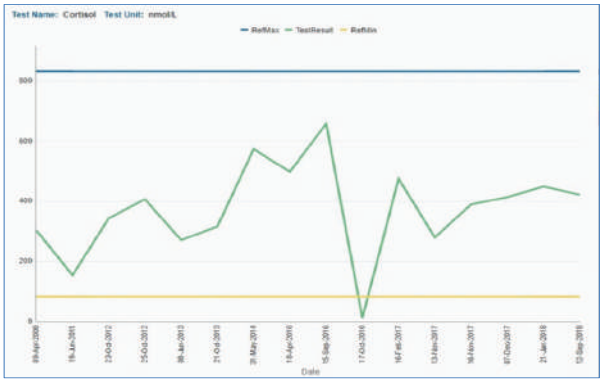

Figure 1: Varying Levels of Serum Cortisol

The patient developed Cushingoid features (buffalo hump with an exponential increase in BMI). Lab investigations revealed prolactinemia (34.7ng/ml) and the patient was commenced on cabergoline 0.5 mg once weekly. MRI pituitary revealed left lobe pituitary microadenoma measuring 3 mm in diameter with a deviation of the pituitary stalk to the right side, see figures 2 (A and B). Adrenal CT revealed left adrenal gland incidentaloma (measuring 1.3 cm in diameter), see figure 3.

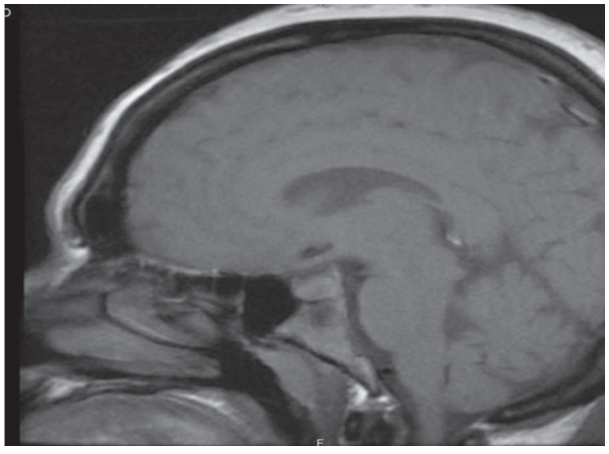

Figure 2 (A): MRI Pituitary (Sagittal View) Revealing Left Lobe 3mm Pituitary Microadenoma

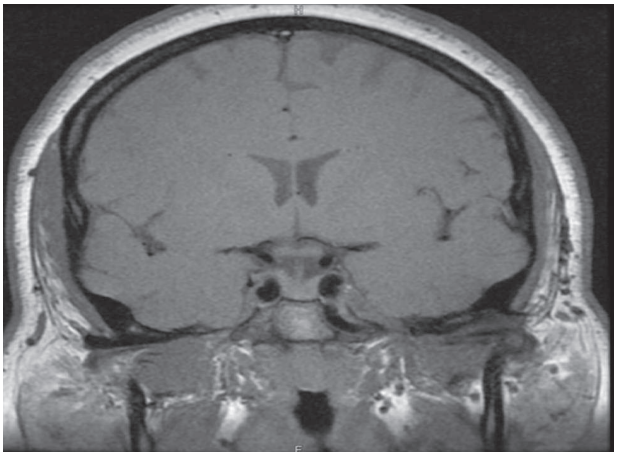

Figure 2 (B): MRI Pituitary (Coronal View) Revealing Stalk Deviation to Right Side

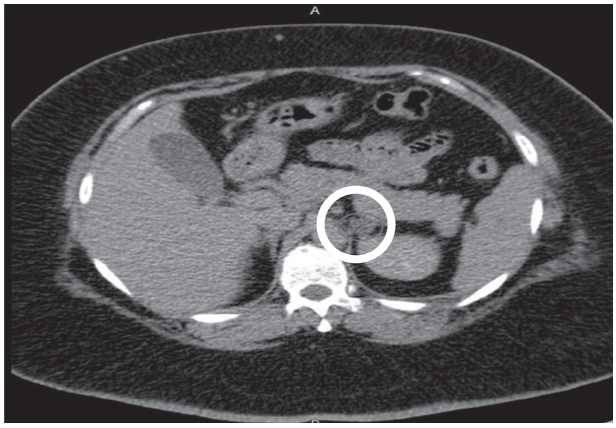

Figure 3: CT Adrenal Revealing 1.3cm Left Gland Incidentaloma (Lesion Encircled)

The case required various specialties to achieve a diagnosis: an endocrinologist, a radiologist and surgeon. The final impression was pituitary hypercortisolism. The patient opted to seek a further medical opinion in a specialized center for surgical intervention.

DISCUSSION

Patients with signs and symptoms consistent with Cushing's syndrome but with normal laboratory values of ACTH and cortisol levels should have a high suspicion index of Cyclical Cushing's syndrome. Factitious and pseudo-Cushing states must be ruled out with Desmopressin (DDAVP) test.[6]

Studies revealed a positive correlation between Cyclical Cushing's syndrome with pituitary-dependent Cushing's disease. The proposed mechanism is that most cases of endogenous hypercortisolism are pituitary in origin or due to a central effect causing rhythmic secretion.[7]

Contrary to popular belief, studies have shown that cyclicity is not an uncommon phenomenon in patients with Cushing's disease, a prevalence of 15%. In a clinical study, it has been observed that females have a higher predisposition to cyclicity; however, no difference in sex was noted between the 'cycling' and 'non-cycling' patients[8].

Multiple testing is required to assess for hypercortisolism, especially with fluctuating clinical signs and symptoms of hypercortisolism[9]. The mainstay of a diagnostic strategy in Cyclical Cushing's syndrome is a long period of surveillance and careful monitoring of both clinical and laboratory findings; which would help to reveal the cyclicity of Cushing's syndrome. Midnight salivary cortisol and 24-hour urine free cortisol testing are more reliable than dexamethasone suppression testing for screening Cyclical Cushing's syndrome[10].

In a recent study, a 28-day collection of night salivary cortisol and early morning urine was performed in patients with confirmed or suspected of Cushing's syndrome. Results revealed normal salivary cortisol correlated well with early morning urine; all cases of cyclical Cushing's were detected[11].

Moreover, in a retrospective, observational study of both cyclical and non-cyclical cases of Cushing's disease revealed that repeated measurements of late-night salivary cortisol are a more sensitive method than urinary free cortisol in establishing Cyclical Cushing's disease, a sensitivity of 88%[12].

It has been proposed that early morning first-voided urine free cortisol to creatinine ratio is a simple, more convenient, repeatable test to diagnose cyclical Cushing's syndrome if compared to 24-hour urinary free cortisol[7,13].

Simultaneous bilateral inferior petrosal sinus sampling is a crucial investigation in the workup of hypercortisolism to differentiate between a pituitary or ectopic origin, a sensitivity of 88-100%[14]. It is reserved for patients with both clinical and biochemical evidence of hypercortisolism, as it does not differentiate between states of pseudo-Cushing's and episodic or Cyclical Cushing's syndrome.

CONCLUSION

Cyclical Cushing's syndrome poses a diagnostic challenge to clinicians. Awareness of various hypercortisolism manifestation helps in guiding physicians with the appropriate management approach. Treatment depends on the underlying cause. Increased recognition has led to enhanced detection and diagnosis of Cyclical Cushing's syndrome.

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