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Cyclic Cushing Syndrome, an Enigma in Diagnosis- A Case Report

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Abstract Cyclic Cushing syndrome is a rare disorder, characterized by repeated episodes of cortisol excess interspersed by periods of normal cortisol secretion. We report a 15-year-old boy with clinical Cushing syndrome and intermittent central Adrenocorticotropic hormone(ACTH) hypersecretion for a period of 8 years. Periods of hypercotisolemia as evidenced clinically and/or biochemically alternated with periods of eucortisolemia leading to much diagnostic dilemma. Ultimately, we were able to demonstrate the episodes of three peaks and two troughs of cortisol secretion favoring our diagnosis. His initial sellar MRI was negative, later high resolution dynamic sellar MRI unmasked a Pituitary micro-adenoma. In the absence of consensus for trans-sphenoidal adenomectomy (TSA) medical management in the form of sodium valproate was prescribed. At present he is on regular follow-up with marked clinical improvement.

Keywords: *Cyclic Cushing syndrome, ACTH, MRI negative Cushing disease*

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1. Introduction

Harvey Cushing described the first case of Cushing's syndrome with a severe phenotype in 1912. Since that time, investigation and management of Cushing's syndrome has remained a significant clinical challenge. Cyclical form of Cushing syndrome presents a unique subset of patients that has important clinical implications. A high index of suspicion of the syndrome is required in patients with symptoms or signs of Cushing syndrome but with normal cortisol values, in patients with fluctuating cortisol values, and in patients with aberrant responses to dexamethasone suppression test. Because of possible variations in steroidogenesis the results of dynamic suppression test in Cushing syndrome must also be interpreted cautiously [1].

2. Case Presentation

We present the case of a short and obese boy that posed a great diagnostic challenge because of variable & conflicting clinical/biochemical picture. A 15-yr-old boy presented to the department of Endocrinology, BSMMU, Dhaka, Bangladesh in 2015 with the complaints of progressive weight gain for 8 yrs and recurrent passage of stone per urethra over last 3yrs. He was diagnosed as a case of Cushing disease in 2010 on the basis of typical clinical & hormonal profile. Investigations done at that time showed evidence of hypercotisolemia (plasma basal cortisol -522 and 956.8 nmol /L on two occasions) with loss of circadian rhythm (morning and evening plasma cortisol-552 and 549 nmol/L respectively), elevation of 24-hr-urinary free cortisol (UFC) approximately 1.5 times the upper limit of normal (281.6 µg/ day) with non-suppressed plasma ACTH (33.4pg/ml). Overnight low dose dexamethasone suppression test (LDDST) showed a positive response (plasma cortisol-420nmol/L). MRI of brain (1.5 Tesla, non-contrast and static) done on that occasion was unremarkable. He was labeled as MRI negative Cushing disease and discharged subsequently with nifedipine as anti-hypertensive with ketoconazole as inhibitor of steroidogenesis. Six to seven months later, he discontinued the drugs by himself finding no appreciable clinical improvement. In the following year he was re-evaluated and high plasma basal cortisol (1216.29nmol/L) with non-suppressed plasma ACTH (28.4pg/ml) in the backdrop of bilateral adrenal hyperplasia as revealed by CT scan of abdomen went in favor of Cushing disease albeit MRI negative. During next 3 years he experienced bouts of renal colic leading to stone impaction in urethra on two occasions that were removed surgically in 2012. Investigations done at that time showed multiple renal calculi with recurrent urinary tract infection, plasma basal cortisol on one occasion was found to be normal (456nmol/L).Subsequently, he was lost to follow up for Cushing syndrome until his admission this time in 2015. Physical examination revealed a well co-operative boy with somewhat chubby appearance. His height: 146 cm (<5thpercentile), body mass index: 30kg/m^2 (>75thpercentile), waist circumference: 94 cm, calculated mid parental

height: 168.5 cm. Sexual maturation rating (SMR) by Tanner staging correlated well to his chronologic age {axillary and pubic hair- Sparse (P2), SPL- 8 cm (G3), volume of testes- 8ml each (G3)}. He had a typical Cushingoid habitus having a BP 130/90 mmHg (on anti-hypertensive). There were widespread fungal infection all over the trunk, the striae however were whitish rather than red/purplish and there was no evidence of skin thinning, easy bruising or proximal myopathy. Fundoscopic examination showed grade-II hypertensive retinopathy. Other systemic examinations were unremarkable. Investigations that were done during this admission showed evidence of impaired glucose tolerance (IGT), dyslipidemia and urinary tract infection. Hormonal assay showed, 24-hr-UFC only marginally elevated (216 µg/ day), plasma ACTH normal (39.5 pg/ml). There was complete suppression of plasma cortisol following overnight LDDST (47nmol/L), USG of kidneys with suprarenals was unrevealing. In the context of florid clinical presentation yet fluctuating hormonal profile and at times paradoxical response on dynamic suppression test, all evidence pointed towards cyclic Cushing syndrome. He was re-admitted five months later and the investigations were repeated. This time the reports corresponded to period of hypercotisolemia (basal cortisol at 9am: 1046 nmol, plasma ACTH: 69 pg/ml, 24-hr-UFC: 385 µg/ day). Finally high resolution (3 Tesla), dynamic, contrast MRI of the Pituitary gland was done that unmasked a Pituitary micro adenoma with partial empty sella. Due to lack of consensus regarding surgical procedure, he was managed medically with sodium valproate, a presumed inhibitor of CRH and is on regular follow-up showing noticeable improvement.

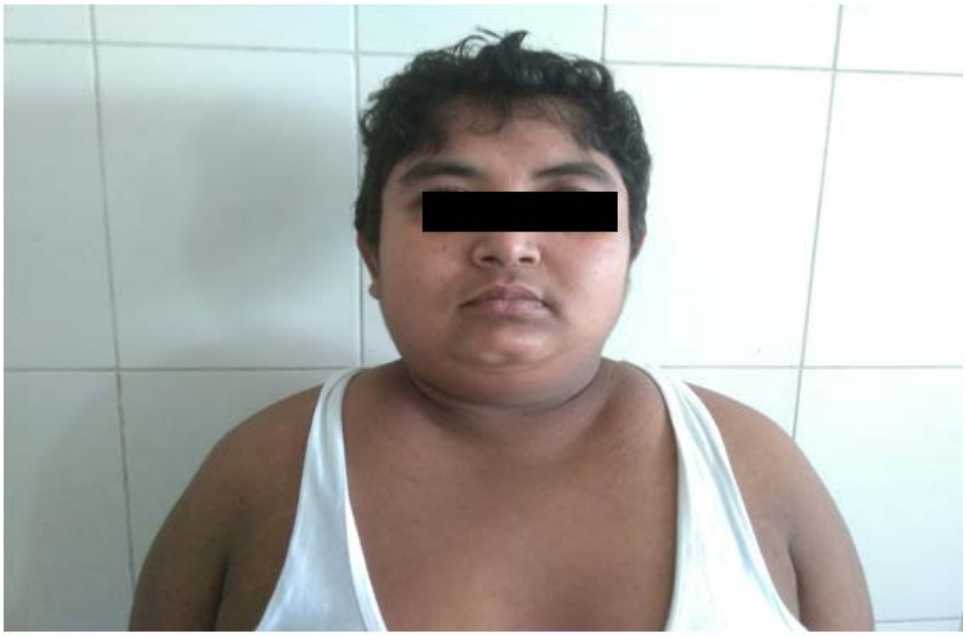


Figure 1. Front profile showing plethoric moon face, supraclavicular fat pad

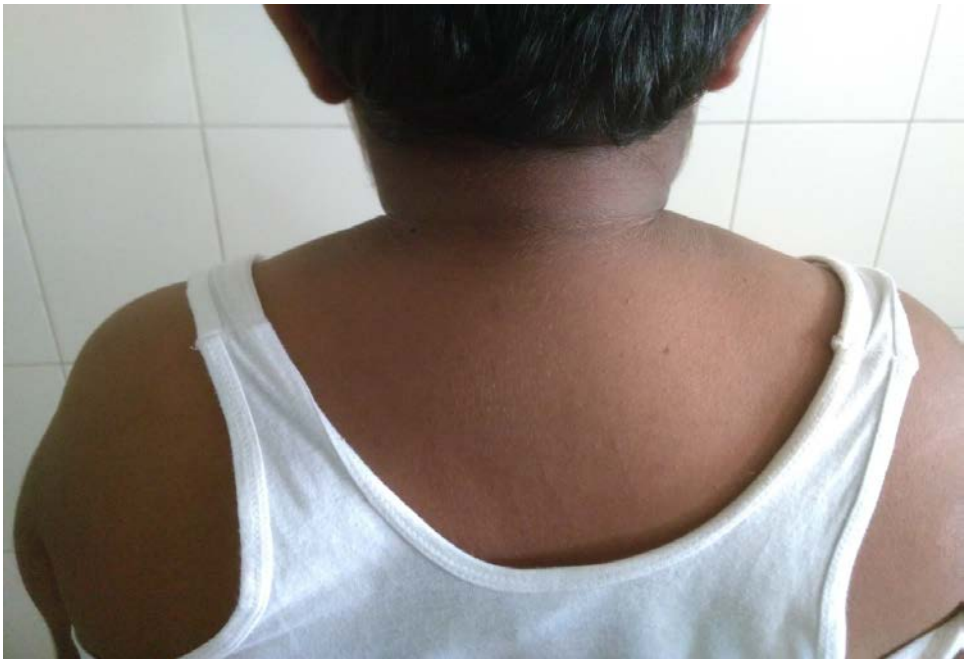


Figure 2. Back profile showing acanthosis nigricans, buffalo hump

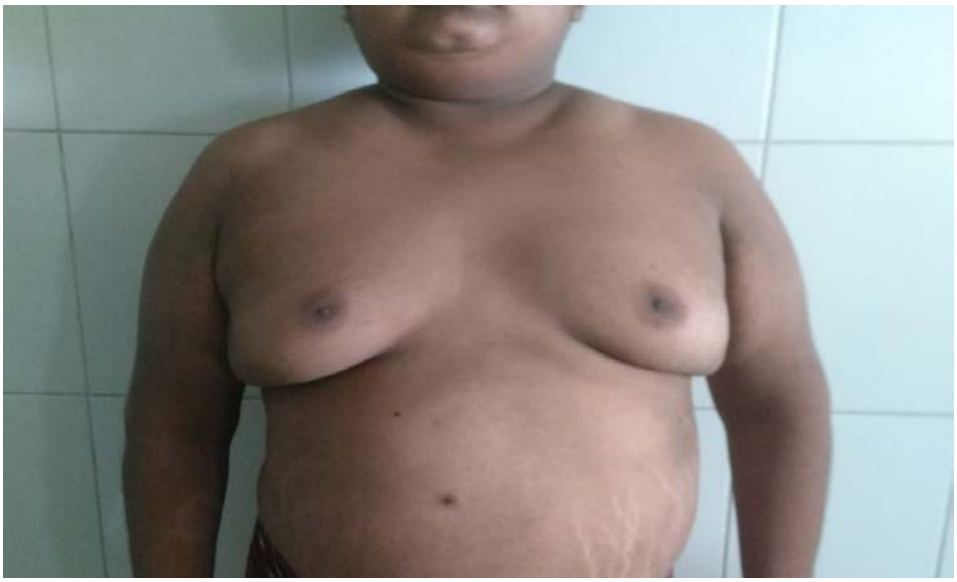


Figure 3. Central obesity, lipomastia and vertical, whitish striae

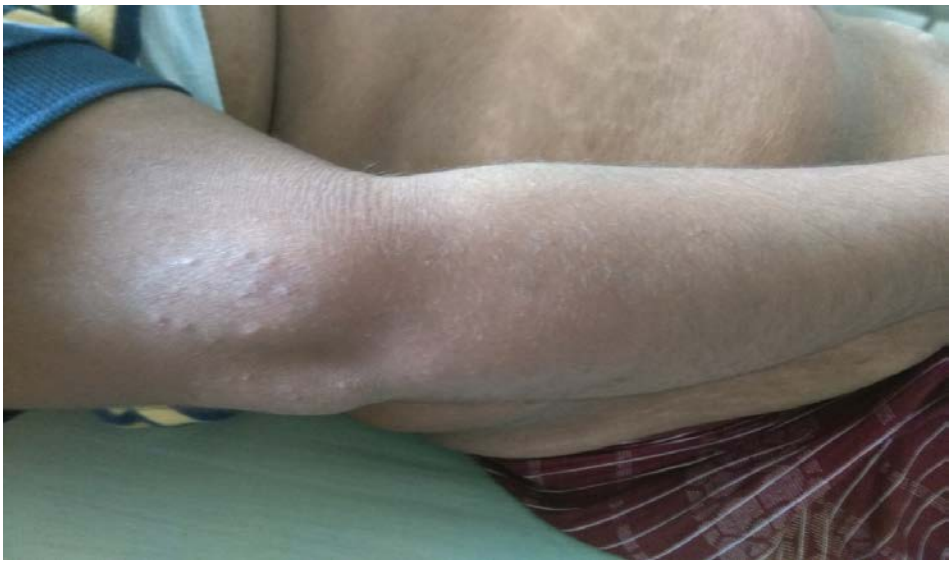


Figure 4. Evidence of Taenia corporis over elbow

CT scan of the abdomen (**2011**)

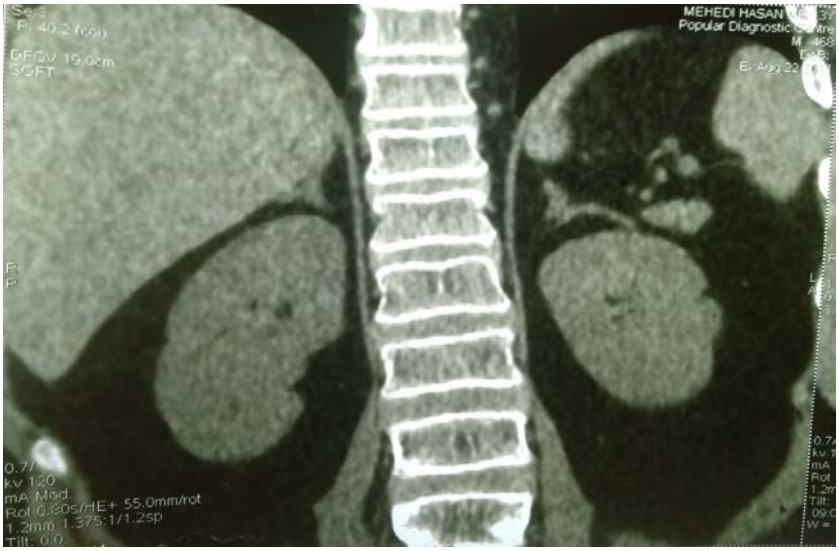


Figure 5.

CT scan of the abdomen (**2011**)

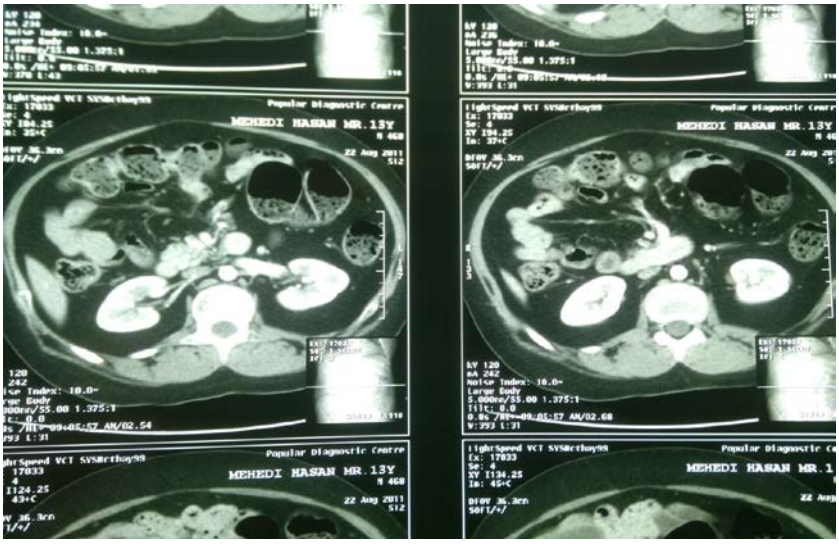
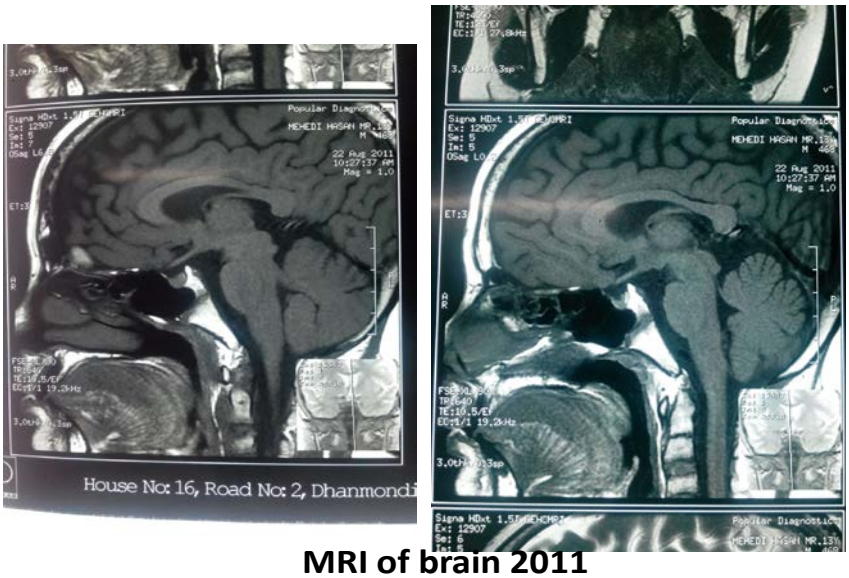


Figure 6.



MRI of brain 2011

Figure 7.

MRI of Pituitary gland (**2015**)

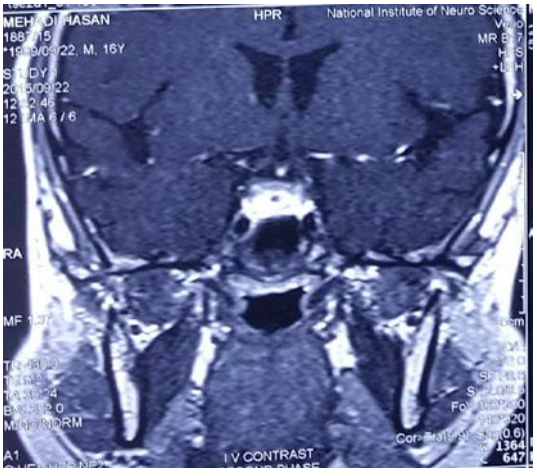


Figure 8.

Table 1. Hormonal profile and radiologic imaging report from 2010-2015

Investigation profile	2010	2011	2012	2015(April)	2015(September)
Serum basal cortisol (normal range 138-690nmol/L)	522 956.8	1216.29	456		1046
24-hr-UFC (normal range 50-190 mcg/day)	281.6			216	385
Plasma ACTH(normal range 0-46 pg/ml)	33.4	28.4		39.5	69
Overnight LDDST(< 50 nmol/L)	420			47	
Evening serum cortisol	549				
MRI of brain	normal	normal			
CT scan of abdomen	normal	Bilateral adrenal hyperplasia			
USG of whole abdomen				normal	
Dynamic pituitary MRI					microadenoma

3. Discussion

Cyclic Cushing's syndrome (CS) is a rare disorder, characterized by repeated episodes of cortisol excess interspersed by periods of normal cortisol secretion. The so-called cycles of hypercortisolism can occur regularly or irregularly with intercyclic phases ranging from days to years. To formally diagnose cyclic CS, three peaks and two troughs of cortisol production should be demonstrated. In a small subgroup of patients with Cushing syndrome (CS), cortisol secretion is only periodically increased. This phenomenon of intermittent hypercortisolism – also called cyclic CS – may be easily missed in clinical practice with consequential treatment delay [2]. It is more common in children than in adults [3]. Cyclic CS may be either of the two different forms of CS (ACTH-dependent or -independent CS). Clinically, it may present with one or many symptoms, depending on the duration of disease activity and the timing of the fluctuations. In the vignette presented above a boy of 15 years was repeatedly evaluated for evidence of hypercortisolism. The diagnosis initially was elusive because clinical and hormonal profiles were fluctuating and at times paradoxical response followed dynamic tests, ultimately after a period of 8 years cyclic Cushing syndrome was established on the basis of demonstration of three peaks and two troughs of cortisol secretion.

A serotoninergic influence, cyclic changes in central dopaminergic tone, spontaneous episodic hemorrhage in the tumor, and the action of inflammatory cytokines with antitumor properties is some of the mechanisms suggested to explain the physiopathology of this phenomenon but the exact mechanism remains to be clarified [3].

The most frequent causes of cyclic CS are associated with ACTH-secreting pituitary adenoma [4,5,6,7], but it has also been reported in association with a well-differentiated neuroendocrine tumor (typical bronchial carcinoid) and malignant carcinoid tumor of the lung [8,9], oncocytic carcinoid of the kidney [10], bronchial adenoma [11], ectopic ACTH secretion by a pheochromocytoma [12], adrenal adenoma13and rare forms of the pigmented variant of micronodular adrenocortical hyperplasia (primary pigmented nodular adrenocortical disease, or PPNAD) [14]. Our patient biochemically had central ACTH dependent Cushing syndrome. Initially labeled as a case of MRI negative Cushing disease, repeat high resolution dynamic Pituitary MRI ultimately unveiled a Pituitary micro adenoma. One interesting phenomenon observed in our case was recurrent, symptomatic nephrolithiasis .Patients with active Cushing disease have an increased prevalence of nephrolithiasis compared with general population, which decreases but not disappears in patients successfully cured from the disease. This complication is likely caused by the synergic effect of different hypercortisolism-dependent metabolic and hemodynamic abnormalities, among which systemic arterial hypertension and excessive urinary uric acid excretion seem to play a pivotal role [15].

Patients suspected of having cyclic CS, significant clinical clues of periodic hypercortisolism are gathered from the history and from subtle clinical findings. Though a rare entity, a number of cases of CS have been described in the literature [16,17,18].

A long period of surveillance as well as careful interpretation and reevaluation of clinical and laboratory findings may be needed to demonstrate the cyclic nature of CS. Salivary cortisol samples collected over time in an outpatient setting are a highly efficacious, noninvasive way of establishing the diagnosis of cyclic CS. Repeating measurements of urinary free cortisol and/or salivary cortisol levels during months to years; attempting to establish three peaks and two troughs over time; performing differentiation tests only during phase of cortisol excess are ways to diagnose Cyclic CS.

A number of drugs have been tried with variable success in treatment of CS. Of these bromocriptine-a dopamine agonist, cyproheptadine-a serotonin antagonist and sodium valproate-an anti-epileptic drug are mention worthy. Sodium valproate increase γ- aminobutyric acid in brain that in turns inhibit CRH and ACTH secretion.

The role of TSA in patients with an unequivocal diagnosis of cyclic CS remains uncertain. Beckers et al. [19] and Shapiro et al. [11] have reported that patients with cyclic CS suffer symptom recurrence after TSA. Based on these reports, TSA cannot be recommended as definitive treatment. Prospective studies of patients with a clear-cut diagnosis of cyclic CS will be needed to better define the role of TSA in this setting.

4. Conclusions

Cyclic Cushing syndrome imposes a genuine diagnostic challenge because of fluctuating clinical presentation and discrepant biochemical picture. To make a confident diagnosis careful follow-up over time is mandatory.

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