Paradoxical Cortisol Response to Dexamethasone in Corticotroph Microadenoma: A Useful Feature of Underlying Cyclic Hormonogenesis

Sir,

Endogenous Cushing's syndrome (CS) was diagnosed in a 22-year-old lady with new-onset diabetes mellitus and oligomenorrhea according to the clinical practice guideline of the Endocrine Society [Table 1]. She declined bilateral inferior petrosal sinus sampling (BIPSS). Hormonal parameters at her subsequent follow-up (FU) visits have been summarized in Table 1. Owing to her minimal symptoms, she refused both surgery and ketoconazole therapy. No endogenous hypercortisolemia could be documented during her last visit in December, 2019.

In CD, the setpoint of feedback inhibition of glucocorticoid (GC) on adrenocorticotropic hormone (ACTH) release from corticotrophs is elevated and more than 50% suppression of serum cortisol following high-dose dexamethasone suppression test (HDDST) is seen in 90% of microadenomas and 50% of macroadenomas. Primary pigmented nodular adrenocortical disease (PPNAD) is characterized by paradoxical rise of endogenous cortisol secretion following dexamethasone administration in about 69-75% of cases. Such paradoxical response may also be seen in about 20% cases of adrenal adenoma and very rarely in CD, particularly in corticotroph macroadenoma, and has never been reported in microadenoma.[1,2] We noticed progressive rise of dexamethasone suppression test (DST) cortisol with an increasing dose of dexamethasone, from 1 mg-overnight DST (ONDST) to low dose DST to HDDST during her initial visit, which prompted us to perform the Liddle's test. Paradoxical rise of ACTH following GC administration in CD was demonstrated long back and a number of postulations like periodic hormonogenesis (with purely fortuitous post-dexamethasone response), GC receptor overexpression on pituitary corticotrophs and, dual feedback mechanisms were put forward.[1,3] Cyclic CS is an unusual form of CS, wherein periodic endogenous excess cortisol synthesis is interspersed by episodes of normal/suppressed cortisol secretion. Endogenous hypercortisolemia was documented at the initial and second FU visits, but not at first and third FU visits, suggesting cyclic CS in this lady. Endogenous hypercortisolemia

Table 1: Summary of investigation at initial presentation and follow-up visits

Date	Parameters	Patient's value	Reference value
	Hormonal evaluation at initial visit		
09/08/18	Free thyroxin (FT4)	1.06 ng/dl	0.8-1.8 ng/dl
	Thyroid stimulating hormone (TSH)	4.33 mIU/L	0.7-4.5 mIU/L
09/08/18	8:00 AM serum cortisol	23.42 mcg/dl	6.2-19.4 mcg/dl
09/08/18	8:00 AM plasma ACTH (iced sample)	12.4 pg/ml	7.2-63.3 pg/ml
14/08/18	Midnight sleeping serum cortisol	10.94 mcg/dl	>1.8 mcg/dl: 100% sensitivity for CS>7.5 mcg/dl: 87% specificity for CS
15/08/18	Overnight 1 mg dexamethasone suppression test (DST) cortisol	2.61 mcg/dl	>1.8 mcg/dl: 95% sensitivity and 80% specificity for CS
16/08/18-18/08/18	Low dose (0.5 mg QDS for 2 days) DST cortisol	13.47 mcg/dl	>1.8 mcg/dl: 96% sensitivity and 70% specificity for CS
19/0818-21/08/18	High dose (2 mg QDS for 2 days) DST cortisol	24.31 mcg/dl	>50% suppression from basal value: 80% sensitivity for CD
28/08/18	8:00 AM serum cortisol	23.5 mcg/dl	>50% rise from baseline is considered positive test
28/08/18-02/09/18	Liddle's test cortisol	44.63 mcg/dl	
12/09/18	8:00 AM serum cortisol	22.3 mcg/dl	ACTH increase greater than 50% and a cortisol rise greater than 20% over baseline values are seen in CD
	8:00 AM plasma ACTH (iced sample)	65.9 pg/ml	
	Serum cortisol (15 min post Inj AVP)	29.4 mcg/dl	
	Plasma ACTH (15 min post Inj. AVP)	111.2 pg/ml	
	Dynamic magnetic resonance imaging (MRI) of hypothalamo-pituitary area	Hypoenhancing area measuring 6 mm (transverse) X 4 mm (craniocaudal) in the right half of the pituitary gland with deviation of the infundibulum towards left	
	Computed tomography (CT) scan of the abdomen	Both the adrenal glands appeared slightly bulky	
	CT scan of neck and chest	Negative for any space-occupying lesion	
	Genetic analysis for protein kinase A regulatory subunit 1A (PRKAR1A)	The entire coding region and exon-intron boundaries of PRKAR1A were amplified by polymerase chain reaction (PCR) and sequenced. No pathogenic mutation was identified.	
	Hormonal evaluation at first FU visit		
14/01/19	8:00 AM serum cortisol	7.72 mcg/dl	6.2-19.4 mcg/dl
14/01/19	8:00 AM plasma ACTH (iced sample)	43.8 pg/ml	7.2-63.3 pg/ml
22/01/19	24-hour urinary free cortisol	241.78 mcg/day	58-403 mcg/day
24/01/19	Overnight 1 mg DST cortisol	0.90 mcg/dl	
25/01/19-27/01/19	High dose (2 mg QDS for 2 days) DST cortisol	0.78 mcg/dl	
	Hormonal evaluation at second FU visit		
18/07/19	24-hour urinary free cortisol	687 mcg	58-403 mcg/day
19/07/19	24-hour urinary free cortisol	714 mcg	58-403 mcg/day
20/07/19	8:00 AM serum cortisol	22.34 mcg/dl	4.3-22.4 mcg/day
20/07/19	8:00 AM plasma ACTH (iced sample)	24.4 pg/ml	
20/07/19-22/07/19	Low dose (0.5 mg QDS for 2 days) DST cortisol	16.6 mcg/dl	
20/07/19-25/07/19	Liddle's test cortisol	61 mcg/dl	
15/08/19	8:00 AM serum cortisol	20.4 mcg/dl	ACTH increase greater than 50% and cortisol rise greater than 20% over baseline values are seen in CD
	8:00 AM plasma ACTH (iced sample)	85.2 pg/ml	
	Serum cortisol (15 min post Inj AVP)	29.5 mcg/dl	
	Plasma ACTH (15 min post Inj. AVP)	152 pg/ml	
	Hormonal evaluation at third FU visit		
22/12/19	8:00 AM serum cortisol	6.1 mcg/dl	6.2-19.4 mcg/dl
22/12/19	8:00 AM plasma ACTH (iced sample)	25.2 pg/ml	7.2-63.3 pg/ml
28/12/19	24-hour urinary free cortisol	101 mcg/day	58-403 mcg/day
4/01/20	Overnight 1 mg DST cortisol	0.7 mcg/dl	
04/01/20-6/01/20	High dose (2 mg QDS for 2 days) DST cortisol	0.42 mcg/dl	

subsided spontaneously during the first and third FU visits. An intriguing feature we noticed, was paradoxical cortisol response with dexamethasone during her initial presentation and second FU visit (i.e., during periods of relapse), but adequately suppressed high dose DST cortisol at her first and third FU visits (i.e., during periods of remission). This could be explained by two possibilities: First, the DST tests were performed during the ascending arm of cyclic hormonogenesis and falsely interpreted as positive Liddle's test. Second, the paradoxical cortisol response is seen only during endogenous hypercortisolemia. The presence of a GC positive feedback loop on corticotrophs and simultaneous endogenous hypercortisolemia has been suggested as the underlying cause of such paradoxical response.[4] A period of low endogenous cortisol, as seen during the trough of cyclic CD, probably changes the character of pituitary corticotroph adenoma, that eventually develops a positive feedback response to GC only during subsequent hypercortisolemia in the peak phase of cyclic CS. Exogenous GC administration thus results in paradoxical ACTH-dependent rise in cortisol secretion only during endogenous hypercortisolemia (as noticed during initial visit and second FU visit) and preceding episode of hypocortisolemia is an essential prerequisite to trigger ACTH hypersecretion through a positive feedback loop. Progressive rise in DST-cortisol values with incremental doses of dexamethasone during the evaluation of CS may thus point towards cyclical hormonogenesis in ACTH-producing corticotroph microadenoma.

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Conflicts of interest

There are no conflicts of interest.

Rahin Mahata, Partha Pratim Chakraborty, Anirban Sinha, Animesh Maiti

Department of Endocrinology and Metabolism, Medical College, Kolkata, 88 College Street, Kolkata 73, West Bengal, India

Address for correspondence: Dr. Partha Pratim Chakraborty, Department of Endocrinology and Metabolism, Super Specialty Block (SSB), 4th Floor, Medical College, 88 College Street, Kolkata 73, Kolkata, West Bengal, India.
E-mail: docparthapc@yahoo.co.in

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