

Influence of Vitamin D on Calcium, Parathyroid Hormone, and Lipid Profile Levels among Saudi Females with Type 2 Diabetes Mellitus and Endogenous Cushing Syndrome

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ABSTRACT

Introduction

Cushing's syndrome (CS) is a rare disorder characterized by symptoms and signs of chronic excessive tissue exposure to glucocorticoids, and is associated with high morbidity and mortality if untreated. The excess cortisol state can result from a number of etiologies- both exogenous and endogenous. It can present with varied and non-specific clinical features. Hence having a high clinical suspicion is important and it can be challenging to arrive at an exact diagnosis, which is very important to initiate appropriate treatment. Here, we present a spectrum of endogenous Cushing's syndrome of different etiologies, who presented to us at different age groups and different clinical features.

Description of Cases

The main aim of this article is to understand the different symptoms and signs with which the patients with Endogenous Cushing's syndrome present, the knowledge required to suspect it even in a non-typical presentation, the extensive and laborious work-up done at arriving the diagnosis and localizing the cause, and then finally initiating appropriate treatment. We randomly chose 8 cases of Endogenous Cushing's syndrome of different presentation and etiology, who presented to our Hospital. We had patients whose age ranged from 13 years to 60 years; patients presenting with typical features of Cushing's syndrome to non-specific features and even being asymptomatic. All the cases underwent appropriate and elaborate work-up to arrive at a diagnosis and also to localize the exact lesion. They then underwent appropriate treatment either in the form of surgery (excision of the lesion responsible for the cortisol excess) or medical therapy. The outcome of the patients was good in 6 of these patients, they achieved remission during follow-up.

Conclusion

Endogenous Cushing's syndrome, though rare, is associated with high morbidity and mortality if untreated. A high degree of suspicion and a good clinical examination is required to diagnose Cushing's syndrome especially in non-florid cases and those with nonspecific features. A systematic, orderly evaluation is required to establish the correct diagnosis and to localize the cause, which will help in planning of appropriate treatment.

INTRODUCTION

Cushing's syndrome (CS) is a disorder characterised by symptoms and signs of chronic excessive tissue exposure to glucocorticoids. The clinical features can be varied and non-specific. Common features include truncal obesity, moon facies, increased fat in dorsocervical area, ecchymoses, plethora, striae, proximal muscle weakness, thin skin, pigmentation of skin, osteopenia/ osteoporosis with fractures, avascular necrosis of bone, mood changes, hypertension, impairment of glucose tolerance or worsening of

glycemic control, susceptibility to infections, edema, deep vein thrombosis/ pulmonary thrombo-embolism. Women can present with irregular menstrual cycles and features of hyper-androgenism. The excess cortisol state can result from a number of etiologies- both exogenous and endogenous. Endogenous Cushing's syndrome is broadly classified as adreno-cortico tropic hormone (ACTH)-dependent and ACTH-independent. ACTH- dependent CS is either due to Pituitary adenoma (Cushing's disease, which is the common form of Endogenous CS) or due to ectopic ACTH and rarely ectopic Corticotropin releasing hormone (CRH) syndrome,

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which commonly occurs as a paraneoplastic manifestation. ACTH- independent CS is due to cortisol excess from adrenal origin either in the form of hyperplasia, adenoma or carcinoma. We present a spectrum of endogenous Cushing's syndrome, of different etiologies ranging from a common Cushing's disease to a rare adrenocortical carcinoma and ectopic adreno-cortico tropic hormone (ACTH) syndrome.

CASES

The case details of the 8 patients who presented to us are mentioned in the tables (Tables 1- 3).

DISCUSSION

Cushing's syndrome is a disorder characterised by symptoms and signs of chronic excessive tissue exposure to glucocorticoids. It is a rare disease and the incidence is estimated to be 2 to 10 patients per million populations per year [1].

Exogenous exposure to glucocorticoids account for most of the cases. Among the endogenous causes of Cushing's syndrome, Cushing's disease is the most common followed by adrenal adenomas and carcinomas, ectopic ACTH syndrome and nodular adrenal hyperplasia [2-4]

Cushing's disease is most often caused by pituitary corticotrophmicroadenoma (90%), and macroadenomas account only for about 5-10% [5]. Syndromes associated with Cushing's disease include Multiple endocrine neoplasia 1 (MEN1), Carney complex, McCune Albright syndrome (MAS), familial isolated pituitary adenoma syndrome and rarely Multiple endocrine neoplasia 2A (MEN2A).

Among the adrenal causes of Cushing's syndrome, unilateral diseases like adenoma and carcinoma account for most cases. Other causes include bilateral diseases like primary pigmented nodular adrenal dysplasia (PPNAD), MAS and ACTH-independent

adrenal hyperplasia (AIMAH) [3]. PPNAD is usually associated Carney complex with an inactivating mutation of PRKAR1A gene [6]. AIMAH occurs as a result of expression of legitimate and illegitimate receptors on the adrenal gland which respond to their respective ligands causing excessive cortisol secretion. Recently, inactivating mutation in ARMC5 tumour suppressor gene has been identified in subset of patients with AIMAH [7].

Ectopic ACTH secretion causing Cushing's syndrome is a paraneoplastic manifestation, commonly occurring with small-cell lung cancer, bronchial and thymic NET among other tumours [8]. Ectopic Corticotropin releasing hormone (CRH) secretion is very rare which can also lead to Cushing's syndrome.

The clinical manifestations of Cushing's syndrome can range from mild to severe involvement of multiple tissues and can be non-specific. Common features include truncal obesity, moon facies, increased fat in dorsocervical area, ecchymoses, plethora, striae, proximal muscle weakness, thin skin, pigmentation of skin, osteopenia/ osteoporosis with fractures, avascular necrosis of bone, mood changes, hypertension, impairment of glucose tolerance or worsening of glycemic control, susceptibility to infections, edema, deep vein thrombosis/ pulmonary thrombo-embolism. Women can present with irregular menstrual cycles and features of hyperandrogenism [9].

The diagnostic evaluation of suspected Cushing's syndrome should proceed in a systematic order to rule out exogenous cause, to confirm the cortisol excess state, to categorize as ACTH dependent or independent, and to localize the lesion.

After ruling out exogenous exposure to glucocorticoids with 8am cortisol levels, the screening tests for Cushing's syndrome include ONDST (overnight dexamethasone suppression test), 24 hour urinary free cortisol, LDDST (low dose dexamethasone suppression test) and midnight salivary cortisol. Positive test in any 2 of the

Table 1: Age, sex and clinical features of the cases.

Case	Age	Gender	Presenting Symptoms	Clinical Signs
1	25 years	Male	Weight gain, puffiness of face, abdominal striae and difficulty in climbing stairs since 6 months.	BP-150/94mmHg, Moon face+, Cushingoid striae+, Thin skin+, PMW+
2	33 years	Male	Uncontrolled glycemic status, resistant hypertension and bilateral pedal edema since 4months.	BP-160/100mmHg, Moon face+, Cushingoid striae+, PMW+
3	13 years	Male	Weight gain and headache since 6 months	BMI-28.4kg/sq.m, Height- 10 th centile, Moon face+
4	60 years	Male	Weight gain, swelling of lower limbs, and worsening of diabetes mellitus and hypertension.	BP-146/98mmHg, Thin skin+, PMW+
5	16 years	Male	Weight gain and difficulty in walking for 3-4 months. He had previously undergone two surgeries for the excision of left atrial myxomas in the last 3 years.	Moon face+, severe acanthosis+, abdominal Cushingoid striae+, multiple pigmented naevi over his trunk+, PMW+
6	24 years	Male	Referred for a large right adrenal incidentaloma which was detected during evaluation of pain abdomen, had h/o weight gain.	Few Cushingoid striae over both legs+
7	35 years	Female, post-partum	Uncontrolled blood glucose levels and blood pressure, which were detected during pregnancy.	Moon face+, abdominal Cushingoid striae+, ecchymosis+, pigmentation of knuckles+, PMW+. Hypokalemia+.
8	53 years	Male	Referred for facial puffiness, pedal edema and weakness of lower limbs. He was recently diagnosed with poorly differentiated adenocarcinoma of left lung with lymph node metastasis.	Moon face+, ecchymosis+, thin skin+ and PMW+. BP-180/100mmHg, persistent hypokalemia+.
PMW- proximal muscle weakness, BP- blood pressure, BMI- body mass index				

Table 2: Biochemical and radiological findings of the cases.

Case	8am Cortisol (mcg/dl)	ONDST Cortisol (mcg/dl)	LDDST (mcg/dl)	24 hour UFC (mcg/dl)	8am ACTH (pg/ml)	HDDST (mcg/dl)	Imaging	Other tests
1	23.5	16.1	15.4	720	147	4.6	Pituitary microadenoma (4.5 × 3.5 mm)	
2	28.8	34.9	21.7		192	19.4	Pituitary macroadenoma (30 × 33 × 28 mm)	IPSS: localized the source to pituitary, but could not lateralize.
3	24.01	11.6	6.7		56.2	6.3	Pituitary microadenoma (6.8 × 7.8 mm)	
4	23.3	29.53		680	12.3	24.76	Bilateral enlarged adrenal glands	Aldosterone Renin Ratio:125. Saline loading test: S. aldosterone - 19 ng/dl
5	23.6	18.8	31.8		13.8; 12.1	27.1	Normal	Whole body PET scan showed no metabolically active uptake. IGF-1 normal. USG testes normal. Thyroid profile normal.
6	20.8	15.6	21.1		6.3		Right adrenal mass (95 × 86 mm)	Testosterone, DHEAS and androstenedione levels normal.
7	46.8	40.5	40.4		166	28.9	Mass in the anterior mediastinum s/o thymoma	
8	60.7	61.1			80; 179		s/o Malignancy of left lung with lymph node metastasis	11 pm Cortisol: 51.6mcg/dl, MRI Pituitary- normal.

ONDST- Over-night Dexamethasone suppression test, LDDST- Low dose Dexamethasone suppression test, HDDST- High dose Dexamethasone suppression test, UFC- Urinary free cortisol, ACTH- Adreno-cortico tropic hormone, IPSS- Inferior petrosal sinus sampling, PET- Positron emission tomography, IGF- Insulin like growth factor, USG- Ultrasonography, DHEAS- Dehydroepiandrosterone sulphate, MRI- Magnetic resonance imaging.

Table 3: Final diagnosis, treatment given and the outcome of the cases.

Case	Diagnosis	Treatment Given	Outcome
1	Cushing's disease due to Pituitary Microadenoma with Secondary Hypothyroidism and Hypogonadism.	TSS for excision of Pituitary Microadenoma.	Achieved remission after surgery; and had recovery of HPA axis around 12 months post-operatively.
2	Cushing's disease due to Pituitary Macroadenoma with Secondary Hypogonadism.	TSS for excision of pituitary corticotrope macroadenoma under intra-operative MRI guidance.	Achieved remission and good glycemic and blood pressure control.
3	Childhood Cushing's disease due to Pituitary Microadenoma with Secondary Hypothyroidism.	TSS for excision of Pituitary Microadenoma.	Achieved remission after surgery; and had recovery of HPA axis around 8 months post-operatively.
4	ACTH-independent adrenal hyperplasia (AIMAH)- with both Cortisol and Aldosterone excess.	Bilateral adrenalectomy.	Had remission of symptoms. Later started on Steroid replacement therapy.
5	Primary pigmented nodular adrenal disease (PPNAD) associated with Carney's complex.	Initially, he hesitated for Surgery and was started on Ketoconazole. Later, he underwent Bilateral adrenalectomy.	Presently, in remission. Requiring Steroid replacement.
6	Right adrenocortical carcinoma (ACC)	He underwent laparotomy with excision of the right adrenal mass. Histopathology of the lesion- adrenocortical carcinoma with Ki-67 of 7% and Modified Weiss score of 5 out of 7	He was advised additional Medical and Radiotherapy. But the patient didnot accepty it and he had recurrence of tumor with systemic metastasis, to which he succumbed.
7	Thymic carcinoid causing Ectopic ACTH syndrome.	Video assisted thorascopic surgery for removal of mediastinal mass. Histopathology- well differentiated thymic carcinoid with positive ACTH staining on immunohistochemistry	She achieved remission. But later lost to follow-up after 1 year post-op.
8	Poorly differentiated adenocarcinoma of left lung with Ectopic ACTH syndrome.	Because of rapid deterioration of clinical status, he was started on Ketoconazole therapy.	However, he succumbed within few days to complications of Metastatic Ca lung and multi-organ failure.
TSS- Transsphenoidal surgery, HPA axis- Hypothalamo-pituitary adrenal axis, MRI- Magnetic resonance imaging , ACTH- Adreno-cortico tropic hormone.			

above tests confirms endogenous cortisol excess state. If there is discrepancy, then 11pm cortisol may help [10].

Once the diagnosis is confirmed, 11pm or 8am ACTH levels should be measured to categorize the disease as ACTH dependent or ACTH independent. In case of ACTH independent state, the cause for Cushing's syndrome is adrenal and hence imaging of adrenals with CT, MRI, adrenal scintigraphy or FDG-PET helps in diagnosing and localizing the exact cause. In case of ACTH dependent state, the cause is either in the pituitary or an ectopic ACTH/ CRH syndrome. In such cases, pituitary MRI, HDDST (high dose dexamethasone suppression test), CRH stimulation test, BIPSS (bilateral inferior petrosal sinus sampling) and imaging of thorax/ abdomen will help in localizing and identifying the lesion. Rarely, the cause of endogenous Cushing's syndrome may remain un-identified [10].

Treatment of endogenous Cushing's syndrome depends on the etiology. Surgery remains the mainstay of treatment. Other second line therapies include medical and radiotherapy [10].

Surgery is directed towards resection of the tumour- transsphenoidal surgery (TSS) of corticotropinoma in case of Cushing's disease, excision of primary tumour in case of ectopic ACTH/ CRH syndrome and removal of adrenal mass in adrenal adenoma. Unilateral or bilateral adrenalectomy is done in case of malignancy, PPNAD, AIMAH or in case the primary lesion cannot be identified or resected.

Radiotherapy (RT) is an adjuvant therapy in Cushing's disease in those who have failed TSS. It can be employed either as conventional RT or stereotactic radiosurgery. The response is earlier and better in children compared to adults.

Medical treatment is used in those with unresectable tumour, recurrent tumour, those who have contra-indications for surgery, those with non-localized source of Cushing's syndrome, those with mild disease, etc. Drugs acting at different targets are used and they include those that inhibit steroidogenesis like Metyrapone, Ketoconazole, Mitotane and Etomidate; glucocorticoid receptor antagonist like Mifepristone; and agents that modulate ACTH release like Pasireotide, Bromocriptine, Cabergoline [10].

Whatever the modality of treatment employed, the patient should be closely monitored throughout the treatment period and also on a long term period.

CONCLUSION

Endogenous Cushing's syndrome, though rare, is associated with high morbidity and mortality if untreated. Here, we presented different and interesting cases of endogenous Cushing's syndrome ranging from pituitary adenoma (CS), adrenal adenoma and

carcinoma, PPNAD, AIMAH to ectopic ACTH syndromes. A high degree of suspicion and a good clinical examination is required to diagnose Cushing's syndrome especially in non-florid cases and those with nonspecific features. A systematic, orderly evaluation is required to establish a correct diagnosis and to localize the cause, which will help in planning of appropriate treatment. Early diagnosis and management of Cushing's syndrome is important to prevent the associated excess morbidity and mortality.

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