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Challenges in the diagnosis and management of Cushing's disease: A case series

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Abstract

Cushing disease is considered as a rare condition characterized by the increases secretion of the Adrenocorticotropic Hormone (ACTH) due to a pituitary adenoma that ultimately causes endogenous hypercortisolism state by stimulating the adrenal glands. Cushing disease is associated with many complications like short stature, weight gain, osteoporosis, cardiovascular and respiratory disorder which leads to high rates of morbidity and mortality. It is important to diagnose and manage Cushing disease as early as possible in order to implement a treatment plan, to lead a successful prognosis and to decrease the complications. We here present the case series of 4 clients that illustrates some of the challenges in diagnosing and managing patient with Cushing disease.

What is new?

Cushing Disease in Pediatric age group is rare condition and Cushing disease is 3 to 8 times is higher in females. Here we have included a case of Cushing disease in an adolescent boy

Keywords: Cushing's disease; ACTH; Pituitary adenoma; Short stature.

Introduction

Cushing's syndrome is a rare condition in childhood, which is caused by prolonged exposure to excessive glucocorticoids. The incidence of Cushing syndrome in general population is about 2-5 cases per million per year. The most frequent cause of Cushing's syndrome is administration of high physiological doses of steroids, mostly for the treatment of dermatological condition, autoimmune and neoplastic diseases [1]. In children, the most frequent cause of endogenous Cushing's syndrome is Cushing's disease, which is cause by ACTH production from pituitary adenoma and represents approximately 75% of all cases of Cushing's syndrome in children over 7 years [2].

Growth failure and weight gain are frequently observed in subjects with ACTH-dependent hypercortisolism. The most important factor causing growth failure in pediatric Cushing's disease is the overexposure to steroids although other factors can also contribute, simultaneous growth hormone deficiency, both before and after surgery has been described [3].

Identification of Cushing's disease is usually made by a skilled clinician with the help of group of tests to establish a state of endogenous hypercortisolism followed by localization of its source. Management requires an individualized approach and multidisciplinary care. Even after proper therapy, these children require longterm follow up into adulthood to assess growth and routine monitoring for metabolic abnormalities or recurrence of disease [4].

Case 1

15 years old girl, weighting 48 kg presented with complain of progressive weight gain and not gaining height. On examination her BP was at 99th centile and hirsutism, acanthosis, buffalo hump and abdominal straie were noted (Figure 1).

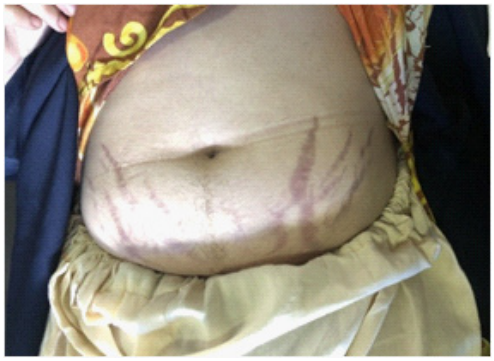

Figure 1: Purple striations.

Her hormonal profile revealed high ACTH of 102 pg/dl, a lack of diurnal variation of serum cortisol with levels of 18.30 ug/dl at 8 AM and 19.70 ug/dl at 8 PM. The serum cortisol levels were not suppressed by low dose dexamethasone, but was suppressed by high dose dexamethasone. Whereas her MRI imaging of brain (Figure 2) was unremarkable. Currently client is on medical therapy and planned for IPPS.

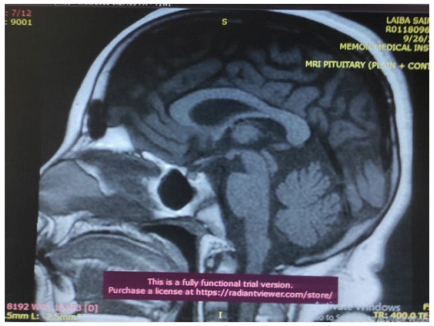

Figure 2: MRI pituitary.

Case 2

A girl of 10 years experienced complain of progressive weight gain and short stature. On examination she was short and hypertensive with truncal obesity, moon facies, hirsutism and buffalo hump.

Laboratory work up showed ACTH levels of 41.6 pg/dl (ND=46.0 pg/ml), and serum cortisol of 22.80 ug/dl at 8 AM and 25.30 ug/dl at 8 PM. Her 24-hour urinary cortisol was high with the values of 403.9 ug/24 hr (20.9-292.3). Low dose dexamethasone suppression test failed to suppress the levels, while high dose dexamethasone suppression test decreased levels of cortisol from 24.20 ug/dl to 0.80 ug/dl. Her imaging of MRI Pituitary was normal, so we went ahead with IPPS which confirmed the diagnosis of Cushing's disease.

She underwent transspenoidal surgery and currently doing well with undetectable ACTH and low cortisol so kept on replacement hydrocortisone.

Table 1:

	RT IPS ACTH	LT IPS ACTH	PERIPHERAL ACTH
PRE INJ VASOPRESSIN	422	1236	173
POST INJ VASOPRESSIN (5 MIN)	287	>1250	229
POST INJ VASOPRESSIN (10 MIN)	>1250	>1250	290

Interpretation:
Central: peripheral ratio 2:1 and after vasopressin 3:1
Intersinus gradient > 1.4 mean lateralizing
This patient has functioning Right and Left pituitary adenoma
She was kept on medical therapy.
She underwent trans spenoidal surgery and currently doing well with undetectable ACTH and low cortisol so kept on replacement hydrocortisone.

Case 3

8 years old girl presented with progressive weight gain. On examinations she had obvious cushnoid features of being short, obese, hirsutism and moon facies.

Her blood chemical analysis revealed serum cortisol levels of 37 ug/dl at 8 AM and while 8 PM levels were 26 ug/dl. An ACTH level of 73.2 pg/dl. Low dose dexamethasone suppression test did not decrease the levels of serum. Whereas high dose dexamethasone decreased levels of Serum cortisol from 26 ug/dl to 1.6 ug/dl. Her 24-hourly urinary cortisol showed high levels of 577.2 ug/24 hr. Her MRI imaging of pituitary revealed a pituitary micro adenoma (Figure 3).

Investigations confirmed Cushing disease. She underwent cyberknife radiation therapy, which showed marked improvement in symptoms. But after 2 years, she again presented with similar complains and MRI was repeated which concluded residual diseases encasing internal carotid artery.

She was kept on medical therapy and bilateral adrenalectomy is advised.

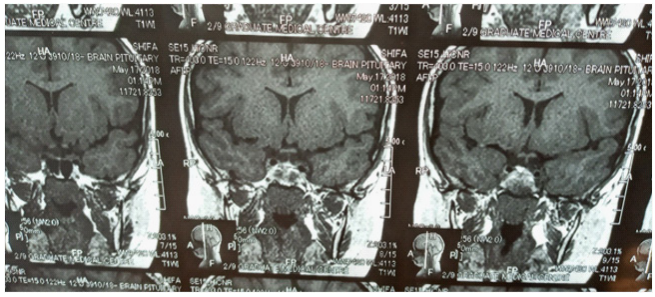

Figure 3: MRI pituitary.

Case 4

9 years old male adolescent presented with complain of increased weight gain, unable to gain height from 2 years & headache, hairs in axilla and public area from few months.

On examination he was short, obese and hypertensive with moon like faces, truncal obesity, buffalo hump, hairs in axilla and pubic area with small penis and bilateral testicular atrophy.

His endocrine workup demonstrated increased ACTH levels

and lack of changes in diurnal serum cortisol level with 32.00 ug/dl at 8 AM and 30.90 ug/dl at 8 PM. A low dose dexamethasone suppression test reduced his cortisol level from 31.5 ug/dl to 1.9 ug/dl. However, MRI brain and pituitary gland showed pituitary Micro adenoma measuring 0.9 x 0.7 x 0.4 mm. A diagnosis of Cushing disease is made and patient was referred to radiosurgery where he went under Gamma knife radiotherapy with total dose of >24.00 Gy. The sign and symptoms improved and patient is on follow up.

Discussion

Endogenous Cushing's syndrome is a rare endocrine disease which is caused by excessive secretion of adrenocorticotrophic hormone in about 80% of cases, usually by a pituitary adenoma also called Cushing's disease, less commonly by an ectopic ACTH syndrome and very rarely by ectopic corticotrophin releasing hormone.

In Cushing's disease, increase adrenocorticotropic hormone secretion results in excess cortisol secretion from adrenal gland. The normal cortisol feedback mechanism of the hypothalamic-pituitary-adrenal axis is disturbed with loss of circadian rhythm result in hypercortisolism state. Clinical features of excessive cortisol include fatigue, weight gain, muscle weakness, hypertension, mood instability, purple skin striae, easy bruising, acne, hirsutism, menstrual irregularities and infections.

These clinical features may vary from patient to patient and its is associated with mortality and morbidity due to systemic steroid excess [5].

Screening tests are used in Cushing's disease to identify the excessive secretion of cortisol, loss of diurnal variation of ACTH and cortisol, urinary free cortisol over 24 hours, salivary cortisol by night and overnight dexamethasone suppression test. The confirmatory test include evaluation of sellar region by using magnetic resonance investigation, IPSS with desmopressin or CRH and overnight dexamethasone 8 mg test. It is also important to perform the confirmation and screening tests in stress-free conditions, avoiding non-specific stimulation of the pituitary-adrenal axis [1].

Cushing's disease treatment aims to improve clinical manifestations. The current treatment and management of the pituitary adenomas is multimodal, including elective surgery, radiation, and drug therapy as supporting treatments. As a last step, bilateral adrenalectomy could be considered in treating the Cushing's disease [1,6].

Learning points

Cushing's Disease (CD) is rare in the pediatric age group, but may present a diagnostic and therapeutic challenge.

It may sometimes present with vague symptoms of fatigue, weakness and mood instability.

It is vital to diagnose Cushing's disease as early as possible and to implement a treatment plan to lead to a successful prognosis and a low number of complications.

Table 2:

	Case 1	Case 2	Case 3	Case 4
Morning cortisol	18.30 ug/dl	22.8 ug/dl	37 ug/dl	32 ug/dl
Evening cortisol	19.70 ug/dl	25.30 ug/dl	26 ug/dl	30.90 ug/dl
ACTH	102 pg/ml	41.6 pg/ml	73.2 pg/ml	103 pg/ml
Urinary cortisol	-	403.9 ug/24hr	577.2 ug/24hr	-
Low dose Dexa suppression test	Not suppressed	Not suppressed	Not suppressed	suppressed
High dose Dexa suppression test	Morning cortisol=28.30 ug/dl After test =1.20 ug/dl	Morning cortisol =24.20 ug/dl After test=0.80 ug/dl	Morning cortisol =26 ug/dl After test =1.6 ug/dl	
MRI pituitary	Normal twice	Normal	Initial normal Rescan=pituitary adenoma	Pituitary micro adenoma
US abdomen	Normal	Normal	Normal	Normal
IPSS	-	IPPS suggestive of Cushing disease.	-	-

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