ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

Case report of Cushing's disease due to pituitary microadenoma presented with psychoses after successful transphenoidal surgery.

Dr. Md. Hamid Ali[1], Dr. Kapildev Mondal[2], Dr. Arijit Sinha[3], Dr. Soumabrota Dutta[4]

1&2- R.M.O. cum Clinical Tutor, Department of General Medicine, Murshidabad Medical College and Hospital

3- Assistant Professor, Department of General Medicine, IDBG HOSPITAL

4. MBBS General Practitioner

Manuscript Info

Manuscript History:

Received: 12 December 2014
Final Accepted: 12 January 2015
Published Online: February 2015

Key words:

ACTH- Adreno corticotrophin hormone, TLC-Therapeutic life style changes, IFG: Impaired fasting glucose

Corresponding Author

Dr. Md. Hamid Ali

Abstract

A 50 years female presented with long term morbid obesity with knee pain and long standing hypertension which is often gets uncontrolled every few months interval. She had very mild IFG that was culminated to the obesity. Patient was more concerned about the obesity which is posing her problem. Patient had so many common problems affecting the general population such as obesity, hypertension and IFG that is why patient was undiagnosed for years. Patient was treated by anti hypertensive medication, diet control, TLC for many years before she came to specialist consultation few months back. Patient was diagnosed a case of Cushing disease due to pituitary microadenoma which was successively removed by transphenoidal surgery. She was losing weight but developed depression with anxiety neurosis one month after surgery that is vey uncommon.

INTRODUCTION

Cushing's disease is caused by an ACTH-secreting pituitary adenoma. This serious endocrinopathy is a subset of Cushing's syndrome which refers to elevated blood cortisol levels. Cushing's syndrome results from tumorso of the pituitary, adrenal glands or from tumors elsewhere in the body (ectopic ACTH producing tumors),See Table-1. The cause of Cushing's syndrome is a pituitary adenoma in over 70% of patients. Most ACTH adenomas are microadenomas. Cushing's disease is relatively uncommon, affecting 10-15 of every million people each year, and most commonly in adults aged 20-50 years old; women account for over 70% of cases. Given that Cushing's disease causes so many common problems affecting the general population such as obesity, hypertension and diabetes, it is possible that many patients with Cushing's disease are undiagnosed for years or perhaps never diagnosed.

Abbreviations: ACTH, adrenocorticotropic hormone; AIMAH, ACTH-independent macronodular hyperplasia; PPNAD, primary pigmented nodular adrenal disease.

Clinical summary: A 40 years female presented with long standing hypertension and obesity. History of weight gain of 20 Kg over the past 7 years along with facial puffiness and easy bruising.. History of hyperpigmentation of face & limbs which has been progressive for the last 7 years. Patient had Impaired fasting Glucose tolerance. She

had no difficulties in exertion. She had knee pain due to obesity. On physical examination patient had buffalo hump, facial puffiness (moon face) and total obesity not only truncal obesity. No striae were seen. No history of hirsutism. She had muscular weakness, fatigue but no muscle wasting. including amenorrhea and decreased libido. There was no history of headache, vomiting, blurred vision, constipation, cold intolerance, voice change or menstrual disorders.

Investigation summary: Weight-85 kg, BP-150/90, Hb-13.1gm%, PPBS-236 mg/dl, Na-135 mEq/L, K-4.2mEq/L, basal cortisol-29.37µg/dl, midnight cortisol- 20.17 µg/dl, ONDST-12.98 µg/dl, HDDST-1.81 µg/dl, 24 hour urinary free cortisol(UFC)-677 µg/day. ACTH- basal-87.8microgram /ml, midnight ACTH-79.6 pg/ml. Her biochemical tests were suggestive of Cushing's disease and she underwent MRI pituitary fossa which showed evidence of pituitary micro adenoma (delayed enhancing lesion in the pituitary measuring 5 mm). Glycaemic control was achieved by oral antidiabetic medications Glimiperide and Metformin. Hypertension was managed by losartan 50 mg BD. She underwent Transseptal Transphenoidal approach and excision of pituitary adenoma successfully. She was maintained on OAD-Glimiperide and Metformin, Antihypertensive-Losartan 50 BD, tapering dose of Prednisolone until maintenance dose of Prednisolone 2.5 -5 mg/day. After 7 postoperative days her basal cortisol came down to 5 µg/dl and ACTH came down to 9,3pg/ml. After 3 months of follow up 15 kg body weight was reduced But she felt depression after the operation which is very uncommon. For that she was given S-Citalopram 10 mg at night. Now she feels better. She is now having no problem and she is doing well.

Discussion & literature review:

Table -1. Causes of Cushing's Syndrome[19]	**Female:Male Ratio**	**%**
ACTH-Dependent Cushing's		**90**
Cushing's disease (= ACTH-producing pituitary adenoma)	4:1	75
Ectopic ACTH syndrome (due to ACTH secretion by bronchial or pancreatic carcinoid tumors, small cell lung cancer, medullary thyroid carcinoma, pheochromocytoma and others)	1:1	15
ACTH-Independent Cushing's	4:1	**10**
Adrenocortical adenoma		5-10
Adrenocortical carcinoma		1%
Rare causes: PPNAD, primary pigmented nodular adrenal disease; AIMAH, ACTH-independent massive adrenal hyperplasia; McCune-Albright syndrome		<1%

Body changes including weight gain in the face (moon face), above the collar bone (supraclavicular) and on the back of the neck (buffalo hump) are commonly seen in patients with Cushing's disease. Skin changes may include easy bruising, with purplish stretch marks (stria) and red cheeks (plethora) as well as excess hair growth (hirsutism) on the face and body. The high cortisol levels also cause weakness, fatigue and muscle wasting(see table-2). Women may develop menstrual disorders including amenorrhea (absence of menses) and decreased libido. Additional serious consequences may include hypertension, diabetes mellitus, osteoprosis and depression.

Table-2 Signs and Symptoms of Cushing's syndrome[19]

Body Compartment/System	**Signs and Symptoms**
Body fat	Weight gain, central obesity, rounded face, fat pad on back of neck ("buffalo hump")
Skin	Facial plethora, thin and brittle skin, easy bruising, broad and purple stretch marks, acne, hirsutism
Bone	Osteopenia, osteoporosis (vertebral fractures), decreased linear growth in children

Muscle	Weakness, proximal myopathy (prominent atrophy of gluteal and upper leg muscles)
Cardiovascular system	Hypertension, hypokalemia, edema, atherosclerosis
Metabolism	Glucose intolerance/diabetes, dyslipidemia
Reproductive system	Decreased libido, in women amenorrhea (due to cortisol-mediated inhibition of gonadotropin release)
Central nervous system	Irritability, emotional lability, depression, sometimes cognitive defects, in severe cases, paranoid psychosis
Blood and immune system	Increased susceptibility to infections, increased white blood cell count, eosinopenia, hypercoagulation with increased risk of deep vein thrombosis and pulmonary embolism

Patients are often diagnosed with Cushing's disease after several years of symptoms which might include progressive weight gain, new onset hypertension or diabetes and mood changes. Comparison of old and recent photographs will often demonstrate changes in appearance. Unfortunately, the diagnosis of Cushing's disease is often long delayed

Hormonal diagnosis: The first step in diagnosing Cushing's disease is to confirm excessive cortisol secretion which is done by performing a 24-hour urinary free cortisol collection, midnight salivary cortisol test and/or a low-dose dexamethasone suppression test. If blood ACTH levels are elevated or normal, then the source is from either an ACTH-secreting pituitary adenoma or an ectopic (elsewhere in the body) ACTH-producing tumor. A high-dose dexamethasone suppression test and/or petrosal sinus sampling are tests used to distinguish between ectopic ACTH production and pituitary ACTH production (Cushing's disease). Petrosal sinus sampling should never be performed before the diagnosis of ACTH-dependent Cushing's syndrome is established.

Algorithm for management of patient suspected of Cushing Disease[19]

Screening test:

1. 24h urinary free cortisol(UFC) 3* Normal 2. Dexamethasone(DEXA) overnight suppression-plasma cortisol >50 nmol/L at 8 am after1 mg Dexa at 11 pm . 3. Midnight plasma (Salivary) cortisol >130nmol/L. 4. If Further confirmation needed low dose Dexamethasone(DEXA) suppression test-plasma cortisol >50 nmol/L after 0.5 mgq6h*2 days

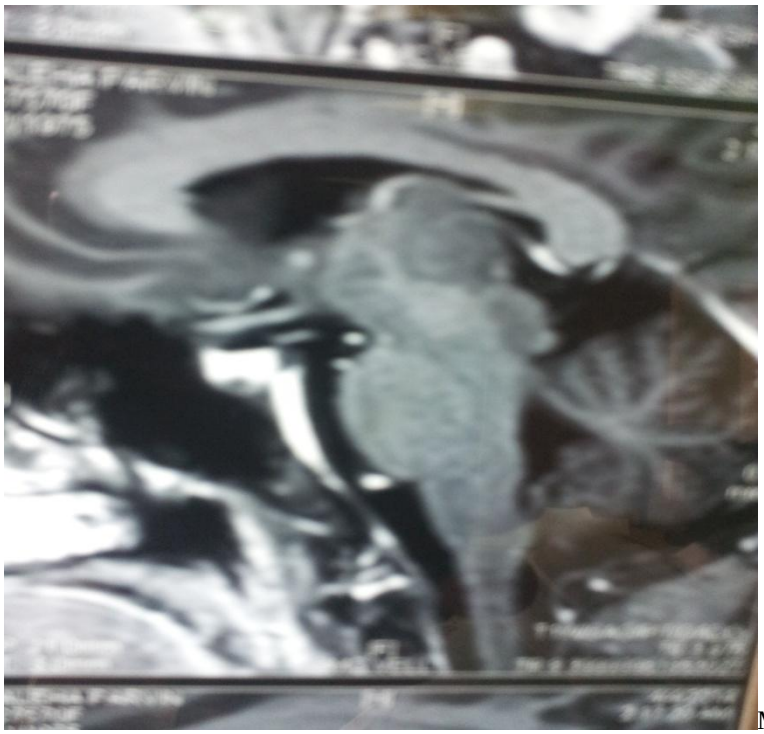
If positive-DD 1- Plasma ACTH

ACTH Normal or >15 pg/ml ACTH dependent Cushing	ACTH <5pg/ml ACTH independent Cushing
1.MRI of Pituitary 2. CRH Test-100 microgram CRH IV , ACTH>40% Cortisol increase >20% 3. High dose Dexamethasone –suppression of cortisol> 50% with 2mg q6h*2days	CT Adrenal 1.Unilateral mass-workout for tumour-unilateral Adrenalectomy 2. Bilateral mass-Bilateral adrenalectomy.
If positive- Cushing Disease-Trans sphenoidal surgery If negative- Ectopic ACTH producing tumour-Selective removal of tumour If unequivocal response-Inferior petrosal sinus sampling (petrosal/peripheral ACTH ratio>2 at baseline and >3 at 5 minutes after CRH 100 µg	

CHR, corticotropin-releasing hormone; DEX, dexamethasone

Imaging: Once the diagnosis of Cushing's syndrome is confirmed hormonally, a pituitary MRI can detect an adenoma in 70-80% of cases. Dynamic post-gadolinium MRI is a recent technique that helps diagnose small

adenomas that may not be seen on a conventional pituitary MRI. CT scans of the adrenal glands are very useful for determining the presence or absence of an adrenal tumor causing Cushing's syndrome.

 MRI BRAIN

Treatment: Cushing's Syndrome: Overt Cushing's is associated with a poor prognosis if left untreated. In ACTH-independent disease, treatment consists of surgical removal of the adrenal tumor. For smaller tumors, a minimally invasive approach can be employed, whereas for larger tumors and those suspected of malignancy, an open approach is preferred.

In Cushing's disease, the treatment of choice is selective removal of the pituitary corticotrope tumor, usually via a transsphenoidal approach. This results in an initial cure rate of 70–80% when performed by a highly experienced surgeon. However, even after initial remission following surgery, long-term follow-up is important as late relapse occurs in a significant number of patients. If pituitary disease recurs, there are several options, including second surgery, radiotherapy, stereotactic radiosurgery, and bilateral adrenalectomy. These options need to be applied in a highly individualized fashion.

1.Endonasal Endoscopic Surgery: Surgical removal is the primary means to achieve long term remission in Cushing's disease; at experienced pituitary tumor centers remission rates range from 80-90% for microadenomas and 30-70% for invasive adenomas or macroadenomas. Because of improved visualization, the endonasal endoscopic approach is rapidly becoming the preferred method for removal of most pituitary adenomas, including ACTH-secreting adenomas. Long-term follow-up with 24 hour urinary free cortisol levels every 6 months is essential to monitor for tumor recurrence which can occur in 5 – 10% of patien

Medical therapy: In some with very severe, overt Cushing's (e.g., difficult to control hypokalemic hypertension or acute psychosis), it may be necessary to introduce medical therapy to rapidly control the cortisol excess during the period leading up to surgery. Similarly, patients with metastasized, glucocorticoid-producing carcinomas may require long-term antiglucocorticoid drug treatment. In case of ectopic ACTH syndrome, in which the tumor cannot be located, one must carefully weigh whether drug treatment or bilateral adrenalectomy is the most appropriate choice, with the latter facilitating immediate cure but requiring life-long corticosteroid replacement. In this instance, it is paramount to ensure regular imaging follow-up for identification of the ectopic ACTH source. Oral agents with established efficacy in Cushing's syndrome are metyrapone and ketoconazole. Metyrapone inhibits cortisol synthesis at the level of 11-hydroxylase (Fig. 342-1), whereas the antimycotic drug ketoconazole inhibits the early steps of steroidogenesis. Typical starting doses are 500 mg/tid for metyrapone (maximum dose, 6 g) and 200 mg/tid for ketoconazole (maximum dose, 1200 mg). Mitotane, a derivative of the insecticide o,p'DDD, is an adrenolytic agent that is also effective for reducing cortisol. Because of its side effect profile, it is most commonly used in the context

of adrenocortical carcinoma, but low-dose treatment (500–1000 mg per day) has also been used in benign Cushing's. In severe cases of cortisol excess, etomidate can be used to lower cortisol. It is administered by continuous IV infusion in low, nonanesthetic doses.

3.Bilateral Adrenalectomy: Removal of the adrenal glands was at one time a preferred method for treating Cushing's disease and lowering cortisol levels. Currently however, this treatment is reserved for patients who have failed prior endonasal transsphenoidal surgery. Although bilateral adrenalectomy has a high success rate in reversing hypercortisolism ranging from 90% to 100%, there is significant risk (25%) of developing Nelson's syndrome with an aggressive ACTH-secreting adenoma. Prior radiosurgery or radiotherapy to the pituitary gland may reduce the risk and delay onset of Nelson's syndrome. The average interval between bilateral adrenalectomy and development of Nelson's syndrome is approximately 5 to 10 years but may be as short as 6 months. Given the long-term risk of Nelson's syndrome after bilateral adrenalectomy is at least 25% and there is a significant risk of major pituitary tumor enlargement, particularly in those with visible adenomas on MRI or CT, use of bilateral adrenalectomy is generally considered a 2nd or 3rd line therapy. After the successful removal of an ACTH- or cortisol-producing tumor, the HPA axis will remain suppressed. Thus, hydrocortisone replacement needs to be initiated at the time of surgery and slowly tapered following recovery, to allow physiologic adaptation to normal cortisol levels. Depending on degree and duration of cortisol excess, the HPA axis may require many months or even years to resume normal function.

Conclusion:

Patients are diagnosed with Cushing's disease after several years of symptoms which were progressive weight gain, long standing hypertension and new onset diabetes and no mood changes. Unfortunately, the diagnosis of Cushing's disease was long delayed 7 years after the symptom. Therefore clinician must search the every cause of obesity before stamping the case as simple obesity otherwise we could miss the many cases of rare disease of Cushing's disease. However the patient was diagnosed a case of Cushing's disease which was successfully treated with transphenoidal surgery. Patient was improving but all of a sudden patient developed depression with strong anhedonia after one month of surgery which is very rare. Usually patient of Cushing's has depression before the diagnosis is made. Here she developed depression after the diagnosis more specifically after surgery. This is the more interesting feature of this case report.

References:

1 Newell-Price J, Bertagna X, Grosmann AB & Niemann LK.Cushing's syndrome. Lancet 2006 367 1605–1617.
2 Reed Larsen P, Kronenberg HM, Melmed S & Polonsky KS.Adrenocortical diseases. In Williams Textbook of Endocrinology, edn 10th, pp 508–525. Ed. PM Stewart, Philadelphia: Pennsylvania,2003.
3 Elte JWF. Diagnosis of Cushing's syndrome. European Journal of Internal Medicine 2006 17 311–312.
4 Castro Cabezas M, Vrinten DH, Burgers JA & Croughs RJl. Central diabetes insipidus and Cushing's syndrome due to ectopic ACTH production by disseminated small cell lung cancer: a case report. Netherlands Journal of Medicine 1998 53 32–36.
5 Chadli A, Alami L, El Aziz S, Lazghad A, El Ghomari H, Kafih M, Essodegui F, Jabri L, Farouqi A & Marouan F. Cushing's syndrome due to a pulmonary carcinoid. Annales d'Endocrinologie 2006 67253–258.
6. Wong CG, Gibson KM & Snead OC. From the street to the brain:neurobiology of the recreational drug gamma-hydroxybutyricacid. Trends in Pharmacological Sciences 2004 25 29–34.
7. Addolorato G, Caputo F, Capristo E, Stefani GF & Gasbarrini G. Gamma-hydroxybutyric acid efficacy, potential abuse, and dependence in the treatment of alcohol addiction. Alcohol 2000 20
217–222.
8. Pistis M, Muntoni AL, Pillolla G, Perra S, Ciqnarella G, Melis M & Gessa GL. Gamma-hydroxybutyric acid (GHB) and the mesoaccumbens reward circuit: evidence for GABA(B) receptor-mediated
effects. Neuroscience 2005 131 465–474.
9. Gonzalez A & Nutt DJ. Gamma hydroxy butyrate abuse and dependency. Journal of Psychopharmacology 2005 19 195–204.

10. Hashiba T, Saitoh Y, Asanuma N, Kouhara H, Maruo T, Fujinaka T,Kasayama S & Yoshimine T. Reduction of a pancreatic tumor after total removal of an ACTH secreting pituitary tumor: differential diagnosis of Cushing's syndrome. Endocrine Journal 2006 53 203–208.
11.Matjeka G, Verges B, Vaillant G, Petit JM, Pacaud A & Brun JM. Food-dependent Cushing syndrome: a new entity of organic hypercorticism. La Revue de Me´decine Interne 1996 17 461–466.
12. Debono M et al: Novel strategies for hydrocortisone replacement. Best Pract Res Clin Endocrinol Metab 23:221, 2009[PMID: 19500765] [Full Text]
13.Arlt W et al: Health status of adults with congenital adrenal hyperplasia: A cohort study of 203 patients. J Clin Endocrinol Metab 95:5110, 2010[PMID: 20719839] [Full Text]
14. Reznik Y, Allali-Zerah V, Chayvaille JA, Leroyer R, Leymarie P, Travert G, Lebrethon MC, Budi I, Balliere AM & Mahoudeau J. Food-dependent Cushing's syndrome mediated by aberrant adrenal sensitivity to gastric inhibitory polypeptide. New England Journal of Medicine 1992 327 1024–1025.

15.Fassnacht M, Allolio B: Clinical management of adrenocortical carcinoma. Best Pract Res Clin Endocrinol Metab 23:273, 2009[PMID: 19500769] [Full Text]
16.Biller BM et al: Treatment of adrenocorticotropin-dependent Cushing's syndrome: A consensus statement. J Clin Endocrinol Metab 93:2454, 2008[PMID: 18413427] [Full Text]
17.Nieman LK et al: The diagnosis of Cushing's syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 93:1526, 2008[PMID: 18334580] [Full Text].
18.Young WF Jr: Clinical practice. The incidentally discovered adrenal mass. N Engl J Med 356:601, 2007[PMID: 17287480] [Full Text].
19.Longo DL, Fauci AS, Kasper DL,Housar SL, Jameson JL, Loscalzo JL Harrison's Principles of Internal Medicine18th edition. www.accessmedicine.com > Chapter 342. Disorders of the Adrenal Cortex >