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Case Report Open Access

Case Report: Differentiating Obesity from Subclinical Cushing's Syndrome

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Abstract

Introduction: There is sustained trend of increased prevalence of obesity all over the world. The main cause is lifestyle, although small percentages of obese patients have additional cause of obesity, e.g. hypercortisolism. Some subtypes of hypercortisolism are more subtle, like subclinical Cushing's syndrome. Such patients have adrenal adenoma with autonomous cortisol secretion, not completely controlled by pituitary. They do not have typical physical features of hypercortisolism. It is impossible to screen all adult obese population for hypercortisolism or to refer them to a specialist Subclinical Cushing has many common characteristics with obesity and it is not easy to discover, might be frequently missed in large mass of "just obese" patients.

Case: 50 years old female patient presented with enormous weight gain of 60 kg in 8 years, unacceptable diabetes control despite insulin/metformin therapy, unregulated hypertension and hyperlipidemia. Lack of suppression in 1-mg overnight dexamethasone test, low morning ACTH and suppressed DHEA-rose suspicion about ACTH independent hypercortisolism. MSCT showed homogeneous low density mass of right adrenal gland measuring 4.9×3.6 cm. Laparoscopic adrenalectomy was performed, PHD confirmed adenoma. Four months after surgery her blood pressure was normal with the same therapy, she lost 17 kg, her lipid panel and diabetes control were significantly better. UKPDS calculated cardiovascular risk for heart disease was 33% and for fatal coronary heart disease 43% lower after surgery.

Conclusion: Patients with subclinical Cushing syndrome are hard to distinguish from other obese people. They have metabolic benefits form surgery followed with lower long term cardiovascular risk reduction. Obese people with diabetes and hypertension that appear suddenly and/or are hard to control might be candidates for screening with 1 mg overnight dexamethasone test, though the best way to differentiate patients with Cushing's syndrome from those with obesity is combined dexamethasone-suppressed corticotropin-releasing hormone.

Keywords: Obesity; Subclinical Cushing's syndrome; Cardiovascular risk; Diabetes

Introduction

Obesity is described as an excessive harmful accumulation of the body fat, defined with body mass index higher than 30 kg/m^2. It is very common disease with sustained trend of increased prevalence in all age groups. In last 40 years obesity has doubled all over the world. Estimation for 2010 showed that 50% of men and women in the WHO European Region were overweight, and 23% of women and 20% of men were obese [1]. An epidemic of obesity was recognized in USA in early 70ies; unfortunately today's situation is even worse than in Europe [2].

Obesity is associated with diabetes, hypertension, coronary heart disease, stroke, hyperlipidemia etc. Those diseases are the main causes of mortality in developed countries and it is not surprising that medical management of obesity becomes a major health concern worldwide. Main cause of obesity is lifestyle, both enhanced calories intake and reduced physical activity.

What's happening with small percentage of obese people having other cause of obesity, e.g. hypercortisolism? Cushing's syndrome is, contrary to obesity, an uncommon disorder with reported incidence of two to three cases per 1 million inhabitants per year [3]. It is not possible to screen a 20-30% of all adult population (obese ones) for such rare condition as hypercortisolism.

There are some subtypes of hypercortisolism that are more subtle, without clear phenotype or typical physical features like subclinical Cushing's syndrome. It occurs in patients with adrenal adenomas and autonomous cortisol secretion, not completely controlled by pituitary. Some reports clamed such condition is more common than we thought; adrenal adenomas were found in autopsies of approximately 3% of patients older then 50 years [4], and up to 20% of them fulfilled criteria for subclinical Cushing's syndrome [5].

Subclinical Cushing has many common characteristics with obesity. It is not possible to refer all obese people to a specialist who is trained to recognize such mild physical changes. Are some subclinical Cushing patients going to be frequently missed in large mass of "just obese" patients? The case of female patient with enormous weight gain, poorly controlled diabetes and hypertension is quite illustrative.

Is Treatment of Subclinical Cushing's syndrome going to help an Obese Patient?

50 years old female patient had in medical history enormous weight gain of 60 kg in 8 years. For last 4 years diabetes was diagnosed, treated with insulin 13 months (metformin plus insulin basal bolus scheme: one basal injection of long lasting insulin analogue at the evening

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ant three boluses of short acting insulin analogues before meals). She has poorly controlled hypertension (treated with combination of AC inhibitor plus thiazide diuretic) and hyperlipidemia (statin therapy). At the first evaluation her weight was 128 kg, height 164 cm, BMI 47.59 kg/m^2. Clinically she was extremely obese, with pale striae on the stomach and some leg edema. There was no muscular atrophy, bruising or plethora. TSH was normal (T4 110 nmol/l TSH 1.57 mIU/L), high HbA1c pointed to unacceptable diabetes control (HbA1c 12, 8%) , despite statins her lipid panel was far out of desirable ranges (LDL 4,10 mmol/L triglycerides 9.06 mmol/L HDL 1,07 mmol/L). After 1-mg overnight dexamethasone suppression test, cortisol value of 165 mmol/L indicated additional work up. Urinary-free cortisol was 299 nmol/L (normal range for the lab up to 416), midnight cortisol 169 nmol/L. At that point she has had only one value out of the range, but due to the clinical presentation additional testing was performed: early morning cortisol was 286 nmol/L (normal range for the lab 138-695), early morning ACTH was 1,4 pmol/L (normal range for the lab 2.2-16.5) and DHEA-S was 0,4 umol/L (normal range for the lab 3-8). ACTH as well DHEA-S were suppressed rising question about ACTH independent hypercortisolism.

After two months a second evaluation was done (in the meantime she gains additional 6 kg). Morning cortisol was 219 nmol/L, midnight cortisol was 113 nmol/L, urinary-free cortisol was 133 nmol/L (all normal ranges). This time post dexamethasone cortisol was 88 nmol/L, ACTH 1.8 pmol/L and DHEA-S 0,5 umol/L. MSCT scan of suprarenal glands showed large homogeneous low density mass -10 HU of right adrenal gland measuring 4.9×3.6 cm in axial plane. Du to those finding laparoscopic adrenalectomy was performed, PHD of the tumor described large adenoma. She has had quick recovery in first 3 days, but on 3rd post-op day symptoms of glucocorticoid withdrawal (muscle pain, weakness) occurred. Those symptoms disappeared after hydrocortisone substitution. Hydrocortisone (same dose of 10+5 mg daily) was tapered gradually later. Four months after surgery her blood pressure was normal with the same therapy, she lost 17 kg, her lipid panel was better and her HbA1c was 10, 7%.

Clinical Feature: Is There A Difference?

There are many identical symptoms, signs and overlapping conditions among obesity and Cushing's syndrome, some of them were present also in described case. Many of them fulfill criteria of metabolic syndrome. The definition of obesity includes weight gain and increased appetite, so it is not possible to use those variables for discrimination. Facial and supraclavicular fullness, even dorsocervical fat pads are present in many obese people. Hypertension, type 2 diabetes/glucose intolerance, hyperlipidemia, polycystic ovary syndrome with acne, menstrual abnormalities and depression are common in population of obese patents and have not high sensitivity.

Signs that appear only in overt Cushing, and are not typical for obesity, have strongest specificity and should be explored [6]. Obese patient frequently have healed silvery striae, usually tiny ones, frequently associated with pregnancy or rapid weight gain. In a case when striae are reddish or livid, wider than 1 cm, present on abdominal wall, when they appear suddenly hypercortisolism should be evaluated. Obese people usually have fat accumulation all over the body, including upper and lower extremities. In a case when there is a muscle weakness of a proximal part of extremities (e.g. difficulty while climbing stairs or getting up from a sitting position) and prominent clinical atrophy screening must be done too. Obese people do not have unusual bruising (therapy with oral anticoagulants must be excluded), but patient with Cushing frequently do. Facial plethora as a sign of hypercortisolism, especially combined with facial rounding is sometimes issue of personal judgment. To be more objective clinician could compare old photographs of the patient over years to demonstrate progression to a Cushingoid state. Sometimes terminal hair hirsutism appears on the face with frontal balding as s result of hyperandrogenism, though this condition is also present in polycystic ovaries. Obese postmenopausal women are less likely to have osteoporosis than women with lower BMI due to endocrine activity of fat tissue. Obese patient with Cushing are prone to osteoporosis and fractures [7]. Patients with hypercortisolism have also higher incidence of thromboembolic incidents.

It is not possible to use clinical differentiation mentioned above for patients with subclinical Cushing's syndrome due to the fact that they have mild changes. One of three criteria for subclinical Cushing's syndrome is actually lack of clear Cushing phenotype (other two are presence of an adrenal adenoma and autonomous ACTH-independent cortisol secretion) [5]. In a study from 2000 by Rossi 50% of such patients were obese, half of them had diabetes and hyperlipidemia, and almost all hypertension [8]. In a study form Mantero from same year and a huge number of patients 41% of them had hypertension, 10% diabetes and 28% of them were obese [9]. In another study by Terzolo from 2002 clear statistical difference among patients with inactive incidentalomas and those with subclinical Cushing's syndrome was postprandial blood glucose and insulin sensitivity, triglycerides level but not BMI [10]. As a conclusion clinical feature of obese patient with subclinical Cushing's syndrome and "just obese" patient is not going to be very helpful in differentiation of those two conditions (Table 1).

How to Screen Subclinical Cushing's Syndrome?

Who should be screened? National Collaborating Centre for Primary Care and the Centre for Public Health Excellence-NICE in their guidelines do not mention screening for hypercortisolism in adults. For children they recommend the endocrine function assessment of some overweight and/or obese children only if they are referred to secondary care [11]. Endocrine Society Clinical Practice Guideline for the diagnosis of Cushing's syndrome do not mention obesity as an indication for screening of adult population (for children indication is decreasing height percentile and increasing weight), and they explicitly recommend against widespread testing [12]. American Association of Clinical Endocrinologists, The Obesity Society, and American Society f or Metabolic & Bariatric Surgery- AACE/TOS/ASMBS in Medical guidelines of clinical practice for the preoperative nutritional, metabolic, and surgical support of the bariatric surgery patients gave statement that routine laboratory testing for rare causes of obesity (for example Cushing's syndrome and other conditions) is not cost-effective and not recommended. It is recommended to do case-by-case decisions to screen based on specific historical and physical findings [13]. Obviously, nobody recommends widespread

Symptom/sign	Obese	Subclinical Cushing	Overt Cushing
Central obesity	+	+	+
Uncontrolled diabetes	+/-	+	+
Uncontrolled hypertension	+/-	+	+
Pale striae	+/-	+	-
Livid striae	-	-	+
Proximal muscle atrophy	-	-	+
Easy bruising	-	-	+
Facial plethora	-	-	+
Osteoporosis	-	-	+

Table 1: Clinical feature of obese patient with subclinical Cushing's syndrome and "just obese" patient.

screening for hypercortisolism, even less for subclinical one. Decision to screen (and when to do it) is exclusively on clinician, based on previous experience and clinical assessment. Since clinical feature of obese patient compared with obese ones having subclinical Cushing's syndrome is not going to be very helpful, perhaps some overlapping conditions could help. History of sudden onset of such conditions (e.g. obese women with normal menstrual cycle suddenly presents with polycystic ovaries), presence of an disease in unusual age (e.g. younger obese person with overt type 2 diabetes), disease that is not easy to control (e.g. hypertension in obese patient poorly treated with combination of few drugs) or combination of signs (e.g. facial fullness in hypertensive patient with diabetes) indicate to screen.

Which test? For the initial testing for Cushing's syndrome there are few test suggested: urine free cortisol, late-night salivary cortisol, 1-mg overnight dexamethasone suppression test DTS and longer low-dose DST (2 mg/d for 48 h) [11].

Urine free cortisol is easy to perform, but in subclinical Cushing's syndrome frequently is not sensitive enough. Late-night salivary cortisol it is not performed routinely everywhere.

The overnight 1-mg dexamethasone suppression test - DST is considered the most valuable screening method with the cut-point of 50 nmol as a confident exclusion. The value among 50 and 138 nmol is considered a "grey zone" that should be retested or evaluated according the clinical presentation [14]. Although higher dose for overnight suppression was not recommended in screening of adrenal incidentaloma [15], it is not easy to say weather 1 mg is enough to screen patient with BMI of 40 kg/m^2 or more. Perhaps, if the patient is morbidly obese 1-mg DST could be skipped and preformed longer low-dose DST (2 mg/d for 48 h) as a first choice.

The best way to differentiate patients with Cushing's syndrome from those with obesity is combined dexamethasone-suppressed corticotropin-releasing hormone (CRH) stimulation test. When the plasma cortisol value (measured 15 min after CRH administration) is greater than 38 nmol/L the test has almost 100% diagnostic accuracy [16]. Although accurate, it is not applicable for screening, and it is not done routinely for big number of obese patients. To verify subclinical Cushing there are few steps more: other tests should confirm at least two abnormalities in hypothalamo- pituitary axis function [8], and vizualise the suprarenal adenoma.

What is Benefit of Adrenalectomy?

There was no doubt that in described case the surgery should be performed due to a tumor mass. Generally accepted recommendation is to remove tumors larger than 6 cm. Lesions that are smaller than 4 cm and defined as low risk (computer tomography low density) by imaging criteria should be followed. For lesions between 4 and 6 cm, either follow-up or adrenalectomy is advised [4]. The question is what to do with the tumor having hormonal characteristic of subclinical Cushing's syndrome and a smaller size. In a study form 2010 Chiodini et al. recommended adrenalectomy to all patients with subclinical Cushing's syndrome and all patients with nonsecreting adenomas smaller than 4 cm [4]. In a recent recommendation form 2011 a simple strategy for subclinical Cushing' syndrome was proposed [17-19]. If the patient is more than 70 years observe, if the age is less than 50 years operate. In the age group between 50 and 70 years consider comorbidities (longstanding vs. recent onset, stable vs. worsening, well-controlled vs. difficult to control).

What was the long term benefit of surgery in the patient described in his case report? To estimate benefit of surgery UKPDS risk formula was applied (calculating cardiovascular risk for next 10 years in diabetic patient). The formula uses variables of age, duration of diabetes, sex, presence of atrial fibrillation, ethnicity, smoking, HbA1c, systolic blood pressure, total cholesterol and HDL cholesterol. Cardiovascular risk with variables before surgery showed that 10 year risk (with 95% confidence interval, adjusted for regression dilution) for coronary heart disease was 17.5 %, for fatal coronary heart disease 11.7 %, for stroke 2.5% and for fatal stroke 0,5%. Cardiovascular risk with variables after surgery showed 10 year risk for coronary heart disease of 11.2 %, for fatal coronary heart disease 6.7 %, stroke 2.3 % and fatal stroke 0,3 %. Her risk for coronary heart disease in next 10 years was 33 % lower, and her risk for fatal coronary heart disease in next 10 years was 43 % lower after surgery.

Conclusion

It is very hard to differentiate obese patients from obese one with mild form of hypercortisolism. Clinical presentation is not going to be helpful, but comorbidities like diabetes and hypertension that appear suddenly and/or are hard to control indicate screening. The overnight 1-mg DST is still considered the first choice for screening of subclinical Cushing's syndrome, though higher dosages of extremely obese patients could be used. Obese patients with subclinical Cushing's syndrome may have many metabolic benefits form surgery and finally lower long term cardiovascular risk. In a decision to perform a surgery age, size of adenoma, presentation of comorbidities and overall risk of operative procedure (anesthetic challenge of obese person) should be taken into consideration.

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