Turkish Journal of Endocrinology and Metabolism, (2006) 2 : 29-33 **REVIEW**

Subclinical Autonomous Glucocorticoid Hypersecretion

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Subclinical autonomous glucocorticoid hypersecretion (SAGH) occurs in patients who have clinically nonfunctioning adrenal adenomas when cortisol secretion becomes autonomous and dysregulated, not fully restrained by pituitary feedback. Up to 20 percent of patients with adrenal incidentalomas have some form of subclinical hormonal dysfunction and may represent a population at higher risk for metabolic disorders and cardiovascular disease. In most cases the degree of hypercortisolism is only slightly elevated than the physiologic daily production rate of cortisol. Dexamethasone suppression tests (DSTs) were employed extensively to screen for subclinical hypercortisolism in patients who have adrenal incidentaloma. Although adrenalectomy has been demonstrated to correct the biochemical abnormalities, its effect on long-term outcome and quality of life is unknown.

Keywords: Adrenal incidentaloma, Subclinical autonomous glucocorticoid hypersecretion, glucocorticoid hypersecretion

Introduction

Adrenal incidentalomas are clinically inapparent adrenal masses. They are discovered inadvertently in the course of diagnostic testing or treatment for other clinical conditions that are not related to suspicion of adrenal disease and, thus, are commonly known as incidentalomas (1,2). These lesions are mostly benign and asymptomatic (3).

During the recent years, with frequent employment of higher resolution, non-invasive imagining techniques, the problem of detection of previously unnoticed masses have arisen. Prevalence has been reported to be 0.35-4.4% with computer tomography, while it is 1.4-5.7% in autopsy series (4). When detected, clinically inapparent adrenal masses raise challenging questions such as whether the lesion is hormonally active or nonfunctioning and whether it is malignant or benign for physicians and their patients. Diagnostic evaluation needs to be performed for these cases and results influence the treatment or follow up plan (5).

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Adrenal masses may be clinically important because some are caused by adrenal cortical carcinomas. Adrenal cortical carcinomas have low incidence rates, approximate 0.5-2 cases per million persons per year and are responsible for 0.2% of cancer deaths in the United States (6). The other clinical concern is hormone overproduction from pheochromocytomas, aldosteronomas, clinical and subclinical hypercortisolism, which may be associated with morbidity if untreated.

Recent reports suggest that up to 20 percent of patients with adrenal incidentalomas have some form of subclinical hormonal dysfunction and may represent a population at higher risk for metabolic disorders and cardiovascular disease. It is important to determine whether groups of patients with subclinical disease benefit from treatment. The term is a wide range of different pathologic entities that share the same path of discovery.

Definition

Subclinical autonomous glucocorticoid hypersecretion (SAGH) occurs in patients who have clinically nonfunctioning adrenal adenomas when cortisol secretion becomes autonomous and dysregulated, not fully restrained by pituitary feedback.

Different terms concluded for this condition such as; Subclinical Cushing's Syndrome, Preclinical Cushing Syndrome, Subclinical Autonomous Glucocorticoid Hypersecretion. Prospective cohort's demonstrated that majority of these cases do not progress to overt Cushing's syndrome therefore it's not a preclinical state. Since subtle autonomous glucocorticoid hypersecretion is associated with long-term morbidity 'subclinical' definition is also questionable. 'Subclinical Autonomous Glucocorticoid Hypersecretion' was concluded in NIH State-of-the-Science Conference Statement in 2002.

The definition of SAGH is based upon fulfillment of two criteria; first, the patient should not present a clear Cushing phenotype, even if some physical findings suggest hypercortisolism such as facial fullness and central obesity. Second the patient should have an adrenal mass that discovered inadvertently in the course of diagnostic testing or treatment for other clinical conditions that are not related to suspicion of adrenal diseases since subclinical hypercortisolism may also be due to pituitary incidentoloma or over replacement of steroid treapy.[2]

Diagnostic Strategies

The degree of hypercortisolism is only slightly elevated than the physiologic daily production rate of cortisol. Loss of circadian rhythm of cortisol was reported frequently (normal circadian rhythm was defined when the cortisol levels decreased by 50% in the evening), despite normal baseline cortisol levels. An increase in urinary-free cortisol excretion was found less frequently, and this confirms the view that measurement of urinary-free cortisol has insufficient sensitivity to detect mild hypercortisolism. Cortisol excess might be minimal but sufficient to suppress ACTH secretion, as low-to-undetectable ACTH levels repeatedly in clinically in apparent adrenal tumors. The response of ACTH and cortisol to CRH also may be blunted in these patients, but CRH challenge did not add significant information to baseline ACTH levels (7,8).

A reduction in dehydroepiandrosterone sulfate (DHEAS) concentration could be seen, which is probably one of the most frequent hormonal finding, in patients with benign adrenal incidentaloma (9). Since in different studies it has been shown that androgen-secreting cells are very sensitive to the lack of ACTH stimulation, as DHEAS remains abnormally low for longer period than cortisol after recovery of ACTH secretion following treatment for Cushing's syndrome, it was thought to reflect suppression of ACTH secretion by autonomous cortisol production. But at present there is insufficient information to conclude that low DHEAS concentration is a reliable, indirect marker of autonomous cortisol secretion since conflicting data have come from the studies that correlated DHEAS concentration with other test results probably due to reduced concentrations in an aged population (10).

Dexamethasone suppression tests (DSTs) were employed extensively to screen for subclinical

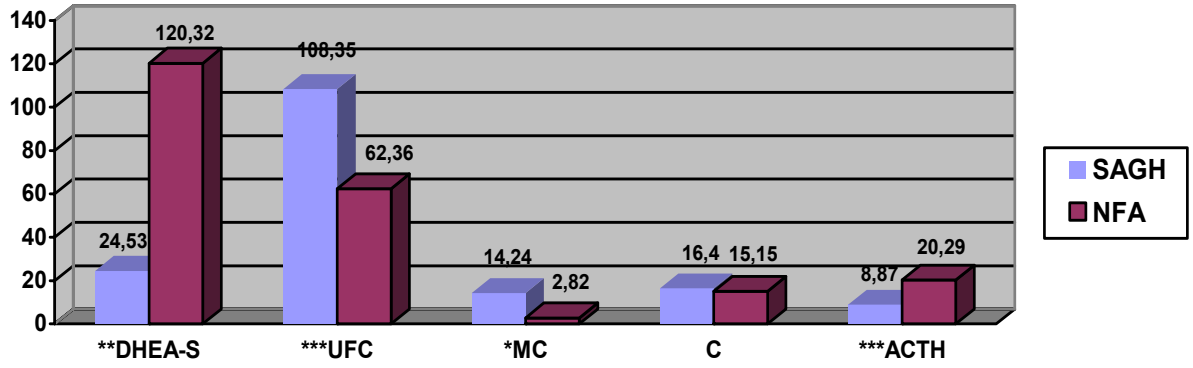

Fig. 1. Comparison of hormonal levels in patients with SGAH and in patients with nonfunctional adrenal masses (Emral R. et al EJE 2003)
Mann Whitney U test, *p<0.001, **p<0.01, ***p<0.05
SGAH: Subclinical Autonomous Glucocorticoid Hypersecretion, NFA: non-functional adrenal adenoma
DHEA-S: Dehydroepiandrosterone sulfate, UFC: Urinary free cortisol, MC: Midnight cortisol, C: Morning cortisol

hypercortisolism in patients who have adrenal incidentaloma. Clinical studies show that the best screening test for preclinical Cushing's syndrome in patients with an incidentally discovered mass is the low dose dexamethasone test. Test protocols, however, differed with regard to dexamethasone dose and threshold value for adequate cortisol suppression. The NIH state-of-the-science conference panel recommended the 1 mg DST as the standard for screening autonomous cortisol secretion. Since Cushing's syndrome is not a consideration to reduce false positive results a higher dexamethasone dose (3 mg or 8 mg instead of 1 or 2 mg) can also be preferred (11). But there has been neither enough experience nor sufficient evidence for higher doses dexamethasone suppression tests. Definition of adequate cortisol suppression by dexamethasone is another controversial issue. The traditional threshold of 5 μg/dl (138 nmol/L) was recommended in the NIH consensus statement. However some experts proposed using lower cut points such as 3 μg/dl or even 1.8 μg/dl to increase the sensitivity of the test since in most healthy subjects, cortisol is barely detectable following 1 mg of dexamethasone. Specificity, however, decreases when lower postdexamethasone cortisol values are used, which may yield more false positive test results.

Terzolo et al.	1 mg sup.	Serum cortisol> 5 μg/dl Urine free cortisol ↑
Reinke et al.	3 mg sup	Serum cortisol> 5 μg/dl Confirmation with 8 mg
Tsagarakis	1 mg sup	Serum cortisol>2.5 μg/dl

Fig. 2. Recommendations for screening autonomous cortisol secretion

Functional autonomy of clinically inapparent adrenal adenomas may be detected with iodocholesterol scintigraphy since several studies correlated the scintigraphic pattern of unilateral uptake with cortisol hypersecretion by adenoma. It also reflects adrenal physiological behavior especially in the case of bilateral involving (12). But it's a time consuming and expensive technique with a questionable specificity since increase uptake is a regular finding of the enlarged adrenal tissue (13).

Long term consequences

It is controversial whether patients with subclinical autonomous glucocorticoid hypersecretion are associated with long-term morbidity and whether treatment to reverse subtle glucocorticoid excess is beneficial.

Data exist that indicate that some patients with subtle glucocorticoid excess may develop metabolic derangements, including insulin resistance, that could be attributable to autonomous cortisol hypersecretion, or, rarely, to overt Cushing syndrome. The long-term effects of these derangements on the patient are unknown. With no doubt many patients who have clinically inapparent adrenal adenoma can suffer the long term complications of cortisol excess, such as hypertension, obesity, diabetes which causes cardiovascular morbidity and mortality. In cross-sectional studies the authors recently demonstrated that patients with adrenal adenoma of incidental discovery with subclinical autonomous glucocorticoid hypersecretion frequently display some features of the metabolic syndrome, such as impaired glucose tolerance, increased blood pressure, and high triglyceride levels. Significant inverse correlation was documented between values of the OGTT-derived insulin sensitivity index and midnight serum cortisol concentrations (14). This study showed subtle autonomous cortisol secretion of these adrenal adenomas share similar features with metabolic syndrome that may cause an acquired condition of insulin resistance in otherwise normoglicemic and nonobese subjects. With these findings hypothetically subclinical Cushing's syndrome may be associated with the clinical phenotype of the metabolic syndrome.

On the other hand Reinke et al. formulated an alternative hypothesis. They observed a proliferative effect of insulin on adrenal cancer line without any effect on cortisol synthesis and suggested that hyperinsulinemia may have a pathological role since it also occurs in polycystic ovary syndrome (15). However it has not yet to be shown that insulin is able to promote adrenal growth.

Tauchmanova et al found that 28 of 126 subjects whom had adrenal incidentaloma and met the criteria for SAGH, sustained an adverse cardiovascular and metabolic risk profile because of

elevated blood pressure, greater waist-to-hip ratio, higher triglycerides, total and low-density lipoprotein (LDL) cholesterol and fibrinogen levels, elevation of the homeostasis of IGT or diabetes mellitus compared with matched controls. The impact of these abnormalities upon vascular system was documented by significant changes in carotis intima media thickness (16).

Although it is well known that overt glucocorticoid excess affects bone metabolism and mass, the effect of subclinical hypercortisolism on bone tissue is still not completely understood since there is not enough evidence and the data differs on bone mineral density in patients who have inapperent adrenal adenoma. In a study it's been reported that the patients who have SAGH had reduced bone mass, altered osteoblastic activity in eugonadal and hypogonadal subjects compared with healthy individuals and with nonsecretory adrenal incidentaloma cases (17). In a prospective study from Turkey in which 70 subjects with adrenal incidentaloma investigated, no difference in bone mass density was determined between patients with subclinical hypercortisolism and non secretory adrenal incidentaloma cases.

The risk of progression from subclinical to overt Cushing's syndrome is unclear. Many studies demonstrate that it occurs rarely in a percentage ranging from 0-12.5% in different studies (in the study of Barzon et al. it was reported that they found the estimated cumulative risk to develop overt Cushing's syndrome 12.5% after one year when considering only patients with subclinical autonomous glucocortiocoid overproduction)(18). In the literature a small adrenocortical carcinoma evolving after diagnosis of subclinical Cushing's syndrome in a patient with an apparently benign adrenal incidentaloma has been reported (19). Also it has been reported that spontaneous normalization of subclinical hypercortisolism in some patients is possible. But the outcome of patients with subclinical hypercortisolism isn't clear since most of these studies have an insufficient follow-up period and have small sample size.

Management strategies

A review of more than 1300 adrenal masses in non-surgical series in the last 10 years shows the incidence of malignant neoplasms is significantly higher for masses greater than 4 cm in size. Surgical excision is recommended for these cases. But before the operation screening the mass for hormonal hyperfunction especially for clinically silent pheochromocytoma and for SAGH are necessary. It is vital for decreasing the risk of preoperative, intraoperative and postoperative complications. Male gender, high age are also predictive for the risk of malignant neoplasms (20). After ruling out the possibility of primary or metastatic malignant lesion, as a central point in the management of adrenal incidetaloma smaller than 4 cm is whether such tumors deserve surgical excision. This decision depends on several variables; one of which is the presence of glucocorticoid excess and its complications. There are reports that unilateral adrenalectomy improves arterial blood pressure, glycemic regulation and weight loss in patients with SAGH. Therefore some authors recommend surgical excision in all patients with subclinical hypercortisolism, if poor control of hypertension diabetes, osteoporosis is present. Although adrenalectomy has been demonstrated to correct the biochemical abnormalities, its effect on long-term outcome and quality of life is unknown.

Screening incidentaloma patients for SAGH preoperatively is also important to determine the increased risk of adrenal insufficiency and the increased risk of flares of the systemic autoimmune diseases postoperatively. Completely asymptomatic patients and very old patients may be treated conservatively, but close follow-up studies then indicated. Patients who are not candidates to surgery should be enrolled in a regular and careful follow-up program to detect, treat and control central obesity, hypertension, glucose intolerance, dyslipidemia, and other manifestations of the metabolic syndrome if SAGH is detected (21).

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