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Case Report: Management of Mild Autonomous Cortisol Secretion

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Abstract **Case Report**

Mild autonomous cortisol secretion is a term used to describe biochemical evidence of abnormal cortisol secretion in patients with ACA, but without the classical external manifestations of overt CS, such as central muscle weakness, adipose tissue redistribution, and skin fragility. ***Materials and methods****:* In this study, we report a case of patient who presents mild autonomous cortisol secretion among incidentally discovered adrenal masses; followed in unit of the endocrinology, diabetology, metabolic diseases and nutrition department of the Mohammed VI University Hospital of Marrakesh. ***Case report*****:** A 68-year-old woman with a history of well-controlled hypertension and diabete presents to our department for etiological assessment of an adrenal incidentaloma. adrenal scan confirms a diagnosis of an incidental right adrenal nodule measuring 27x26mm is also identified having an density of 33UH and washout > 50%, the patient's physical examination is unremarkable and she does not have any overt Cushingoid features or midline back pain or paroxysmal attacks. Biochemical investigations revealed a morning cortisol following 1 mg of dexamethasone is 2 ug/dL. A normal serum potassium and methoxylated derivatives in urine are normal. A diagnosis of a mild autonomous cortisol secretion was made and given the relatively mild degree of cortisol excess and well-controlled Comorbidities a conservative management is chosen, she should undergo annual clinical reassessments. If she develops new or worsening cortisol-related comorbidities, she should undergo further biochemical testing and reconsideration of adrenalectomy. ***Conclusion:*** Future studies with adequate randomization and follow-up to assess adverse clinical endpoints are needed to determine the optimal management and follow-up of patients with MACS.

Keywords: Mild autonomous cortisol secretion, central muscle weakness, skin fragility, adrenal incidentaloma.

INTRODUCTION

Incidentally discovered adrenal tumors are reported in ~ 5% of adults undergoing cross-sectional imaging [1]. It is estimated that annually around 4 million patients in the United States alone are discovered with an adrenal mass, given that 80 million computed tomography (CT) scans are performed in the same period of time [2].

In any patient with a newly discovered adrenal mass, there are two questions that need to be addressed: (i) is the adrenal mass malignant or benign, and (ii) is the adrenal mass hormonally active?

The majority of adrenal tumors are benign adrenocortical adenomas (ACA) diagnosed in 82–88% of patients, while adrenocortical carcinoma or other adrenal malignancy affects 3–12% of patients evaluated in endocrine centers [3-5]. Overt adrenal hormonal excess is demonstrated in ~ 15% of ACA and includes mainly primary hyperaldosteronism and overt cortisol excess (Cushing's syndrome, CS). However, mild autonomous cortisol secretion (MACS) is much more prevalent, affecting up to 48% of patients with ACA [4-6].

Mild autonomous cortisol secretion is a term used to describe biochemical evidence of abnormal cortisol secretion in patients with ACA, but without the classical external manifestations of overt CS, such as central muscle weakness, adipose tissue redistribution, and skin fragility. Various terms have been used to describe MACS, such as "subclinical Cushing's syndrome" and "subclinical hypercortisolism"; however, the term "subclinical" is inaccurate, as these patients present with higher prevalence of adverse cardiovascular risk factors, such as diabetes mellitus type 2(DM2), hypertension, dyslipidemia, obesity [7-9], increased rates ofcardiovascular disease [10, 11],

metabolic bone disease [12], and highermortality rates [10, 13], when compared with patients with nonfunctioning adrenal tumors (NFAT).

MATERIALS AND METHODS:

In this study, we report a case of patient who presents mild autonomous cortisol secretion among incidentally discovered adrenal masses; followed in unit of the endocrinology, diabetology, metabolic diseases and nutrition department of the Mohammed VI University Hospital of Marrakesh.

CASE REPORT

A 68-year-old woman with a history of well-controlled hypertension and diabete presents to our department for etiological assessment of an adrenal incidentaloma.. adrenal scan confirms a diagnosis of an incidental right adrenal nodule measuring 27x26mm is also identified having an density of 33UH and washout > 50%, the patient's physical examination is unremarkable and she does not have any overt Cushingoid features or midline back pain or paroxysmal attacks. Biochemical investigations revealed a morning cortisol following 1 mg of dexamethasone is 2 ug/dL .A normal serum potassium and methoxylated derivatives in urine are normal. A diagnosis of a mild autonomous cortisol secretion was made and given the relatively mild degree of cortisol excess and well-controlled Comorbidities a conservative management is chosen, she should undergo annual clinical reassessments.

If she develops new or worsening cortisol-related comorbidities, she should undergo further biochemical testing and reconsideration of adrenalectomy.

DISCUSSION

MACS is diagnosed in up to 48% of patients with incidentally discovered adrenal tumors following evaluation in endocrine Clinics [14]. As 5% of adults undergoing cross-sectional imaging are discovered with an adrenal mass, the overall prevalence of MACS is potentially ~ 2% of adult population. MACS is usually diagnosed in adults >50 years of age and in a higher proportion in women (60–70%). Patients with MACS commonly present with one or more features of metabolic syndrome (such as hypertension, obesity, and DM2) [15]. Patients with bilateral or larger adrenal tumors (>2.4 cm) are at increased risk of MACS [16, 17], though MACS can be seen in smaller tumors as well. Patients with MACS rarely progress towards overt CS [18], and therefore, MACS is a unique chronic disorder rather than a milder spectrum of CS. In a recent systematic review and meta-analysis of patients with MACS and NFAT, <1% of patients demonstrated progression to overt CS during the mean follow-up period of 4 years. However, new MACS was reported in 5.6% of patients with NFAT, while resolution of MACS was observed in 1.9% of patients [19]; it is unclear whether this can be explained by initial misdiagnosis (false positive testing) or a true change in hormonal production by the adrenal mass. Assessment for MACS should begin with a careful history and examination, recognizing that many patients may have comorbidities associated with Cushing's syndrome but few will have overt manifestations on physical examination [20]. Although no head-to-head trials have directly compared the available screening modalities, the conventionally-accepted standard test for the diagnosis of MACS is the low-dose dexamethasone suppression test (LDDST), whereby 1 mg of oral dexamethasone is given at approximately 11PM and a serum cortisol is measured the following morning [21]. In individuals with normal hypothalamicepituitaryeadrenal axis function, the morning cortisol should suppress to 50 nmol/L (1.8 ug/dL) or lower. Any value higher than 50 nmol/L is suggestive of MACS, with values exceeding 138 nmol/L (5 ug/dL) indicating an even greater degree thereof [21]. Potential causes of false positive testing (i.e. unsuppressed cortisol after the LDDST) include use of cytochrome P450 inducers such as phenytoin or carbamazepine which accelerate dexamethasone metabolism, estrogens (such as oral contraceptives) which increase cortisol binding globulin and total circulating cortisol levels, and obesity. Obtaining a dexamethasone level along with the morning cortisol to ensure that levels are therapeutic can be helpful when interpreting results [22]. An alternative strategy, which the authors of this article frequently use, is to give a higher, 2 mg dose of dexamethasone. Since the objective of the test is to simply assess whether cortisol secretion is independent of circulating ACTH, and not to assess for pituitary Cushing's disease, higher doses of dexamethasone to ensure adequate suppressive levels can minimize the risk of false positives, particularly in obese individuals.

Using a cortisol cut-off of 50 nmol/L to differentiate normal physiology from MACS, the LDDST is up to 100% sensitive, making it an optimal first-line screening test [23]. On the other hand, the specificity of the LDDST at this cut-off can be as low as ~60%, often necessitating the use of other screening methods such as the 24-h urinary free cortisol (UFC) or late-night salivary cortisol (LNSC) to confirm the diagnosis [23]. Indeed, these and other tests including a dehydroepiandrosterone-sulfate (DHEA-S) level and ACTH level may be helpful adjunctive studies if MACS is identified or suspected.

Further assessment should be performed in the patient with a post-LDDST cortisol greater than 50 nmol/L. The European Society of Endocrinology guidelines recommend obtaining a basal morning ACTH and repeating the LDDST in 3e12 months in patients with a post-LDDST cortisol >50 nmol/L and _138 nmol/L, but only in those patients with potential cortisol-related comorbidities such as hypertension or type 2 diabetes [21]. A low or suppressed ACTH,

typically less than ~2 pmol/L (~9e10 pg/mL), further supports a diagnosis of ACTH-independent MACS from an adrenal source. Although potentially helpful when combined with other studies, an ACTH value in isolation has low sensitivity and specificity for the diagnosis of MACS from an adrenal mass. For example, in a recent study of nearly 200 patients with an incidentally discovered adrenal mass, Olsen and others reported that only 53% of patients with a post-LDDST cortisol of _50 nmol/L had a suppressed ACTH (defined as < 2 pmol/L), while 19% of patients with a post-LDDST cortisol of <50 nmol/L also had a suppressed ACTH [24].

Possible explanations for the poor reliability of ACTH in diagnosing MACS include diurnal variation and pulsatility of ACTH, measurement error at low analytical levels, and preserved responsiveness of adrenal adenomas to ACTH [24].

The patient with a post-LDDST cortisol level of >138 nmol/L is regarded as having a higher degree of MACS. The European Society of Endocrinology guidelines recommend screening these patients for associated comorbidities such as hypertension, type 2 diabetes, and vertebral fractures; further tests to ascertain the degree of cortisol excess, including a 24-h UFC, LNSC, an ACTH, and a repeat LDDST, are also recommended [21]. Although it can miss subtle cases of autonomous cortisol secretion from an adrenal mass, 24-h UFC testing using modern liquid chromatography-tandem mass spectrometry (LC-MS/MS) analyticmethods is up to 98% sensitive and 91% specific in identifyingMACS using a cut-off of >170 nmol/24 h [23]. Late-night salivary cortisol testing appears less useful than the LDDSTor 24-hUFC in identifying MACS from adrenal masses, with sensitivity rates of ~20e30% and specificity rates of ~85% [25].

Other ancillary tests may be useful in confirming the diagnosis of MACS from an adrenal mass. DHEA and DHEA-S, the latter ofwhich ismore reliable and reproducible, are adrenal androgenswhose synthesis is entirely dependent on ACTH. Patients with MACS have significantly lower levels of DHEA and DHEA-S than patients without MACS, owing to the relative suppression of ACTH [26]. When DHEA-S levels were normalized to the age- and sex-specific lower limit of the DHEA-S reference range in patients with incidental adrenal masses, one study reported a sensitivity of 99% and specificity of 92% in diagnosing MACS using a cut-off of <1.12 [27]. In recent years, there has been significant interest in measuring plasma and urine multi-steroid panels using LC-MS/MS methods (i.e. steroidmetabolomics) to aid in the diagnosis of MACS. Elevated levels of plasma 11-deoxycortisol, 21-deoxycortisol, 11deoxycorticosterone, corticosterone, and low levels of DHEA-S and androstenedione have been observed in patients with MACS from an adrenalmass, allowing for this distinctive "plasma steroid signature" to correctly diagnose patients in upto 90% of cases [26]. Measurement of 24-h urinary steroid metabolites can provide an even more accurate measure of adrenal steroid production, with elevated glucocorticoid metabolites and suppressed androgen metabolites characteristic of MACS [28]. Although plasma and urine steroid metabolomics hold considerable promise for the diagnosis of MACS in patients with an incidentally discovered adrenal mass, more validation studies are needed before they have a routine role in clinical practice. The available diagnostic modalities for MACS are summarized in Table 2.

Management and follow-up of mild autonomous cortisol secretion Patients with clinical evidence of Cushing's syndrome from an adrenal mass should be treated with surgical adrenalectomy given the clear morbidity and mortality associated with untreated disease [29].

The management of patients with an incidentally discovered adrenal adenoma who do not have overt Cushing's syndrome but who have MACS is more controversial as the available studies comparing outcomes of adrenalectomy versus conservative management have been generally small, observational in nature, and heterogeneous.

A 2016 meta-analysis by Bancos and colleagues examined the role of adrenalectomy across 26 studies with 584 patients with MACS and found that 61% had an improvement in hypertension, 52% had an improvement in diabetes, 45% had an improvement in obesity, and 24% had an improvement in dyslipidemia following surgery [30]. When compared with medical management of the cardiometabolic consequences of MACS (i.e. "conservative management"), the patients who underwent adrenalectomy had a significant relative risk reduction in hypertension and diabetes, but did not have a statistically significant improvement in obesity or dyslipidemia [30]. Adrenalectomy in patients with MACS has also been shown to reduce the risk of vertebral fractures [31], although no trials have demonstrated a reduction in mortality or cardiovascular events. A key limitation to the available evidence on the efficacy of surgical adrenalectomy in MACS is the reliance on observational data that is susceptible to bias and confounding and the use of inadequate reference populations. No robust randomized controlled trials comparing adrenalectomy with conservative management in patients with MACS from an incidental adrenal adenoma have been published, although trials are ongoing Due to the low quality of the available evidence, management of MACS from an incidentally discovered adrenal adenoma should be individualized. Patients who have higher degrees of cortisol excess and multiple or poorly controlled comorbidities potentially related to hypercortisolism may be more likely to

benefit fromsurgical adrenalectomy; offering this approachmay be considered reasonable despite the associated risks and costs. On the other hand, patients withmilder degrees of cortisol excess and fewer comorbidities that are well-controlled may have a less favorable risk-benefit ratio from adrenalectomy. The European Society of Endocrinologyguidelines suggest that patients with post-LDDST cortisol levels of >138 nmol/L who have at least two hypercortisolism-related comorbidities, one of which is poorly controlled, should be offered adrenalectomy whereas patients with post-LDDST cortisol levels _138 nmol/L without any comorbidities should not [21]. However, the choice between adrenalectomy versus conservative management ultimately rests with shared decision-making between the physician and patient, weighing such factors as patient age and preference in addition to the biochemical findings and presence of comorbidities. Demonstration of MACS via multiple laboratory tests can increase confidence of a true biochemical abnormality thatmay warrant surgical intervention. As many as two-thirds of patients with MACS will have postoperative adrenal insufficiency after adrenalectomy from prolonged suppression of the contralateral adrenal gland [32]. Consequently, guidelines suggest empiric intraoperative “stress dosing” of glucocorticoids followed by a postoperative taper, although some clinicians use morning postoperative cortisol levels to guide initiation of glucocorticoids [33, 34]. If surgery is not chosen, conservative management of MACS from an incidental adrenal adenoma usually involves periodic clinical reassessment. Althoughmedical therapy to lower cortisol production is available, it is not typically used to treat MACS; however, administration of timed evening doses of metyrapone has been shown to reset the normal diurnal rhythm of cortisol and potentially decrease markers of cardiovascular inflammation, representing a possible future treatment option [35]. If conservativemanagement is chosen, follow-up should be individualized based on the lack of evidence-based studies. The European Society of Endocrinology guidelines recommend that all patients with post-LDDST cortisol levels >138 nmol/L undergo annual clinical reassessment for new or worsening cortisol-related comorbidities; patients with post-LDDS Tcortisol levels between 50nmol/L and 138 nmol/L in addition to preexisting cortisol-related comorbidities should undergo the same reassessment [21]. Neworworsening cortisol-related comorbidities should prompt additional or repeat biochemical assessment and reconsideration of surgical adrenalectomy. Although some clinicians repeat an annual LDDST, there is no evidence to support this practice in the absence of worsening clinical or biochemical features of hypercortisolism [36]. There is also no evidence to support clinical followup beyond 4 years in the stable patient with MACS from an incidentally discovered adrenal adenoma [21].

CONCLUSION

Future studies with adequate randomization and follow-up to assess adverse clinical endpoints are needed to determine the optimal management and follow-up of patients with MACS.

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