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Management of Adrenal Incidentalomas

European Society of Endocrinology (ESE) Clinical Practice Guideline with The European Network for the Study of Adrenal Tumors (ENSAT)

Editors
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QUESTION 2: IS THE ADRENAL INCIDENTALOMA HORMONALLY ACTIVE?

R 3.1. Every patient with an AI should undergo a careful assessment including clinical examination for symptoms and signs of adrenal hormone excess.

Comment*: Rapidly developing hirsutism or virilization is a clinical indicator for an androgen-producing tumor, and should be addressed by measuring testosterone and androgen precursors, whereas recent onset of gynecomastia should trigger measurement of estradiol.*

R 3.2. All patients with AI should undergo a 1 mg overnight dexamethasone suppression test to exclude cortisol excess (recommendation: strong; quality of evidence: low).

R 3.3. The results of the 1 mg overnight dexamethasone suppression test should be interpreted as a continuous rather than categorical (yes/no) variable (recommendation: strong; quality of evidence: very low). However, serum cortisol levels post dexamethasone ≤50 nmol/L (≤1.8 µg/dL) allow to rule out autonomous cortisol secretion (recommendation: strong; quality of evidence: low).

R 3.4. Post-dexamethasone serum cortisol levels between 51 and 138 nmol/L (1.9-5.0 µg/dL) should be considered as evidence of «possible autonomous cortisol secretion» and cortisol levels post dexamethasone >138 nmol/L (>5.0 µg/dL) should be taken as evidence of «autonomous cortisol secretion». Additional biochemical tests to confirm cortisol secretory autonomy and assess the degree of cortisol secretion might be required. For the clinical management, however, the presence of potentially cortisol-related morbidities and age of the patient are of major importance (Fig. 2).

Comment: *Despite the awareness that in implementing additional diagnostic tests the likelihood of at least one test being a false positive increases, the following steps are suggested:*

- *Measurement of basal morning plasma ACTH and repetition of the dexamethasone test after 3-12 months in all patients with «possible autonomous cortisol secretion» and comorbidities.*
- *In patients with «autonomous cortisol secretion», the additional measurement of 24h urinary-free cortisol and/or late-night salivary cortisol. Since cortisol secretion in patients with «autonomous cortisol secretion» is independent of ACTH, a higher dose of dexamethasone (e.g. 3 mg, 2 x 2 mg or 8 mg) might also be reasonable as additional test.*

R 3.5. «Autonomous Cortisol Secretion» should not be considered as a condition at high risk for the development of overt Cushing's syndrome (recommendation: strong; quality of evidence: low).

Comment: *Studies reporting on follow-up of patients with AI have uniformly found a very low percentage (<1%) of patients with «autonomous cortisol secretion» progressing to overt Cushing's syndrome.*

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R 3.6. Patients with «possible autonomous cortisol secretion» or «autonomous cortisol secretion» should be screened for hypertension and type 2 diabetes mellitus (recommendation: strong; quality of evidence: very low). Treatment should be according to current guidelines for these conditions (recommendation: weak).

R 3.7. Patients with «autonomous cortisol secretion» should be screened for asymptomatic vertebral fractures. This may be done by re-evaluating the available images (if a CT was performed) or by plain X ray. If osteoporosis is present, appropriate treatment should be considered (recommendation: strong; quality of evidence: low).

***Comment**: The panel did not reach consensus on recommending assessment of bone mineral density by dual-energy x-ray absorptiometry (DXA). If there is no likely explanation for the osteoporosis, removal of the adrenal adenoma may be considered.*

R 3.8. The approach to patients with «autonomous cortisol secretion» due to adrenal adenoma should be individualized on the base of age, degree of cortisol excess, comorbidities and patient's preference (recommendation: strong; quality of evidence: very low). In all patients considered for surgery, ACTH-independency of cortisol excess should be confirmed by a suppressed or low basal morning plasma ACTH.

***Comment:** The panel did not reach consensus on indication of surgery for patients with «autonomous cortisol secretion». There is some evidence in the literature of improvement of hypertension, hyperglycemia and dyslipidemia following surgery, but the quality of this data is limited. No data on mortality or major cardiovascular endpoints are available. There was consensus that surgery is indicated in patients with post-dexamethasone serum cortisol >138 nmol/L (>5 µg/dL) and the presence of at least two comorbidities potentially related to cortisol excess (e.g. type 2 diabetes, hypertension, obesity, osteoporosis), of which at least one is poorly controlled by medical measures. Conversely, there is no reason for surgery when post-dexamethasone serum cortisol is <138 nmol/L (<5 µg/dL) and no comorbidities are present.*

3.9. Pheochromocytoma should be ruled out in all patients by measurement of plasma-free metanephrines or urinary fractionated metanephrines (recommendation: strong).

***Comment:** Clinically silent pheochromocytomas may lead to hemodynamic instability during surgical excision. For this reason, metanephrines should be measured even in normotensive patients, and diagnosis of pheochromocytoma should be considered in patients with borderline values of metanephrines and indeterminate imaging features on CT.*

R 3.10. The use of the aldosterone/renin ratio to exclude primary aldosteronism is recommended in patients with concomitant hypertension or unexplained hypokalemia.

R 3.11. Sex hormones and steroid precursors (DHEA-S, androstenedione, 17-OH-progesterone, as well as testosterone in women and estradiol in men and post-menopausal women) should be measured in patients with imaging or clinical features suggestive of adrenocortical carcinoma.

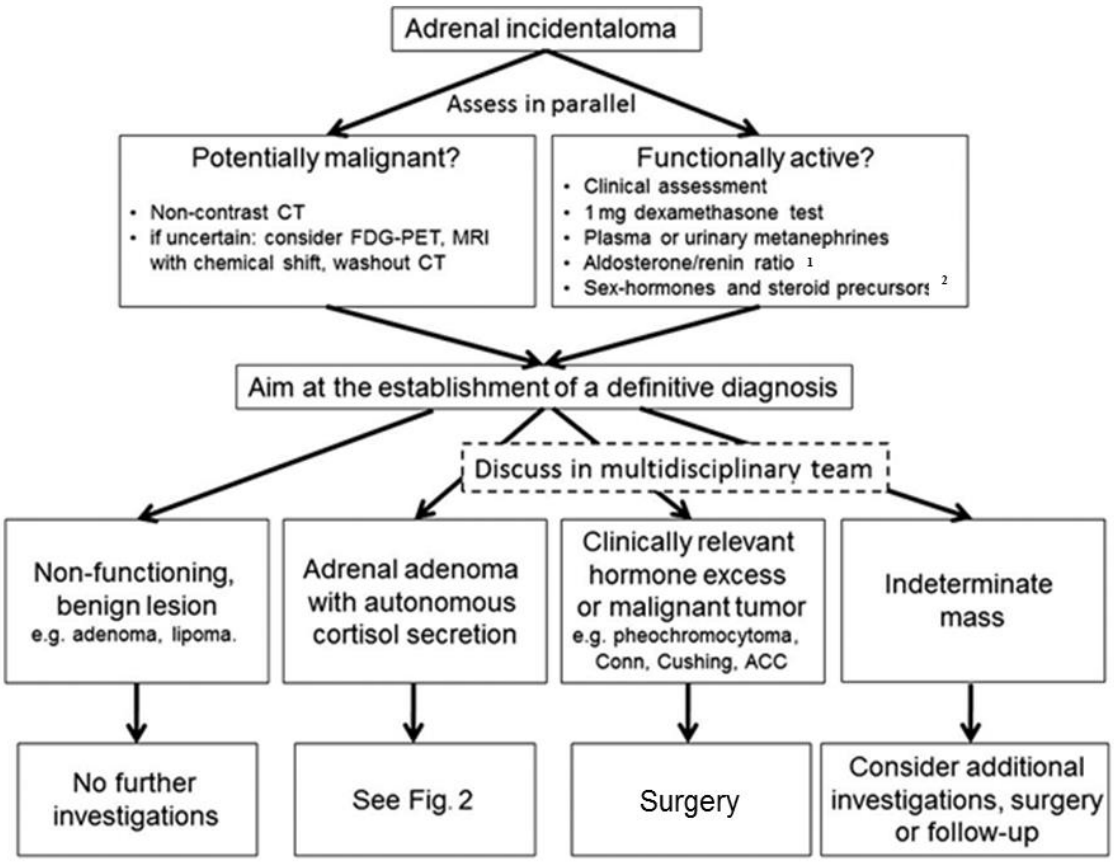

Figure 1
Flowchart on the management of patients with AI
[1]Only in patients with concomitant hypertension and/or hypokalemia.
[2]Only in patients with clinical or imaging features suggestive of adrenocortical carcinoma.

REFERENCE

Fassnacht M, Arlt W, Bancos I, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol 2016, 175: G1-34.