DIAGNOSTIC AND THERAPEUTIC MANAGEMENT OF PATIENTS WITH ADRENAL INCIDENTALOMA

DIJAGNOSTIČKE I TERAPIJSKE MERE LEČENJA PACIJENATA SA ADRENALNIM INCIDENTALOMOM

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Summary

Routine and frequent use of computerized tomography (CT) angiography in vascular disease detection has led to frequent suprarenal gland abnormal findings that could, if undiagnosed, significantly complicate the course of the future treatment. The term adrenal incidentaloma refers to adrenal lesion discovered serendipitously during an imaging investigation. Adrenal incidentalomas do not constitute a single pathological entity. Major concerns are risks of malignancy and autonomous hormone secretion. The majority of all adrenal incidentalomas (approximately 79%) are nonfunctioning benign lesions. Among functioning lesions subclinical cortisol excess is most frequently found. All patients with adrenal incidentaloma should undergo clinical, biochemical, and imaging evaluation for malignancy and hormone production. In this review, we discuss the current issues in diagnostic and therapeutic management of patients with adrenal incidentaloma. Follow-up of patients with adrenal incidentalomas involves the assessment of growth and development of hormonal function. After this review analysis several useful protocols could be designed to help vascular surgeons to adequately treat patients with concomitant vascular disease and adrenal incidentaloma.

Key words: adrenal gland, incidentaloma, tumor, autonomous hormone production, functional testing, imaging.

Sažetak

Rutinska i učestala upotreba kompjuterizovane tomografije (CT) angiografije pri dijagnostici vaskularnih oboljenja dovela je do čestog otkrivanja promena na nadbubrežnim žlezdama koje u značajnoj meri mogu kompikovati ishod lečenja ovih pacijenata. Termin adrenalni incidentalomi se odnosi na adrenalni leziju slučajno otkrivenu tokom imidžing procedura. Adrenalni incidentalomi ne predstavljaju pojedinačni patološki entitet. Najveća briga predstavlja rizik od maligniteta i hormonske aktivnosti. Većina od svih adrenalnih incidentaloma (približno 79%) su nefunkcionalne benigne lezije. Među funkcionalnim lezijama najčešće se susreću pacijenti sa subkliničkim kortizolskim ekscesom. Svi pacijenti sa adrenalnim incidentalomima trebaju biti podvrgnuti kliničkoj, biohemijskoj i imidžing evaluaciji za malignitet i hormonsku aktivnost. U ovom radu mi razmatramo aktuelne dijagnostičke i terapijske probleme vezane za pacijentesa adrenalnim incidentalomima. Praćenje ovih pacijenata obuhvata praćenje rasta i hormonske funkcije adrenalnih incidentaloma. Nakon analiziranja ovog pregleda, moguće je napraviti nekoliko korisnih protokola koji bi pomogli vaskularnim hirurzima u adekvatnom lečenju pacijenata sa udruženim vaskularnim oboljenjima i adrenalnim incidentalomima.

Ključne reči: nadbubrežna žleza, incidentalom, tumor, nezavisna hormonska produkcija, funkcionalno testiranje, imidžing.

INTRODUCTION

Adrenal incidentaloma (AI) is an adrenal mass, generally 1 cm in diameter or larger, discovered through imaging study performed for indications other than evaluation of adrenal disorder. (1) Adrenal incidentalomas are found in the adrenal cortex or medulla and may be hormonally active or nonfunctional, malignant or benign. (2) The prevalence of AI at autopsy was found to be less than 1% in patients younger than 30 years old and up to 7% in patients aged 70 or older. (3) Imaging studies yielded similar findings: AI were found in approximately 2–4% of the middle aged, increasing up to more than 10% in

the elderly, peaking between the fifth and the seventh decade. (4) Because of its increasing prevalence, AI is now recognized as a common clinical problem and has even been proclaimed as “endocrine epidemic of A-I-D-S” – Adrenal Incidentaloma Discovered Serendipitously. (5)

The prospectively validated management of a patient with AI has not been established although a “state of the science statement” and Medical guidelines for the management of adrenal incidentalomas have been published by the National Institute of Health and American

Table 1. Etiology of incidentally found adrenal mass (adrenal incidentaloma)**1. Adrenal cortical lesions**

Adenoma
 Adenocortical carcinoma
 Nodular hyperplasia

2. Adrenal medullary tumors

Pheochromocytoma
 Ganglioneuroma/neuroblastoma

3. Other adrenal tumors

Myelolipoma, lipoma, lymphoma, haemangioma, hamartoma, teratoma

4. Metastasis

Lung, breast, kidney, gastrointestinal tract tumors, lymphoma, melanoma

5. Infection

Abscess, tuberculosis, fungi, cytomegalovirus

6. Infiltration

Amyloidosis, sarcoidosis

7. Cysts and pseudocysts

Parasitic, endothelial, degenerative adenoma

8. Haemorrhage**9. Pseudoadrenal masses**

Stomach, pancreas, kidney, spleen, liver, vascular lesions (e.g. aneurysms and tortuous splenic veins)

Association of Clinical Endocrinologists and American Association of Endocrine Surgeons (AAACE/AAES), respectively. (6,7) The challenge is to recognize and treat an infrequent AI that involves a significant risk, either because of hormonal activity or because of its malignancy. (8) Adrenal incidentalomas do not constitute a single pathological entity. Etiology underlying incidentally discovered adrenal mass is presented in Table 1.

We will discuss the diagnostic and therapeutic approach in the following cases of AI: nonfunctional benign adrenal mass, hormone – secreting adenomas, adrenal nodular hyperplasia, pheochromocytoma and adrenal malignancy.

CLINICAL APPROACH IN A CASE OF AI**Nonfunctioning benign adrenal mass**

Approximately 79% of all AIs are nonfunctioning benign lesions including adrenocortical adenoma, myelolipoma, ganglioneuroma and adrenal cyst. If functional screening is negative, the diagnosis is most likely nonfunctioning adenoma, the most frequently found adrenal tumor of all. (9)

Adrenocortical adenomas usually appear as non – highly vascular, homogenous lesions with smooth, encapsulated margins. In some isolated cases, these lesions progress to functioning tumors. (14)

Imaging studies cannot reliably distinguish between functioning and nonfunctioning adrenal adenomas. The second most commonly found benign adrenal mass is myelolipoma, a tumor consisted of fat and bone marrow elements. Due to its structure myelolipoma presents with characteristic imaging appearance. (9)

Cortisol producing-adenoma

Autonomous cortisol secretion was found in 5.3% of patients with AI. The autonomous cortisol production is referred to as subclinical hypercortisolemia because these patients lack full phenotypic manifestations of Cushing syndrome. However, these patients are more likely to suffer from obesity, hypertension, diabetes mellitus, and osteoporosis. (10) Patients with subclinical hypercortisolemia usually have normal values of morning cortisol level. However, disturbances in the circadian rhythm of cortisol excretion may occur in the form of slightly increased nocturnal cortisol concentrations. (11) Adrenal autonomy is best assessed by dexamethasone suppression test. The test consists of the administration of 1 mg of dexamethasone (3 mg of dexamethasone may be also applied) at 11pm followed by the measurement of morning serum cortisol concentration at 8am. The result of cortisol level greater than 138 nmol/L (5 µg/dL) is standardly used to define autonomous cortisol production. (12) The use of a much lower cut – off level of 50 nmol/L increases the sensitivity, but it also increases the rate of false positive results. (13) The result of <1.8 µg/dL has been proposed as the best negative predictive value.

The following tests can be performed either to confirm or rule out autonomous cortisol production: 2 – day high – dose dexamethasone suppression test, late – night salivary cortisol measurement and 24 – hour urinary free cortisol test. Cortisol value of 70 nmol/L measured after 2 mg daily dexamethasone (for 48h) is used by some as a cut off value for identifying patients with autonomous cortisol secretion. (13) Low adrenocorticotrophic hormone (ACTH) concentration can be found in patients with autonomous cortisol production due to suppression. On the other hand, low dehydroepiandrosterone – sulphate level may also be found as a result of insufficient ACTH production. Adrenal scintigraphy may be used for assessing lesion functionality.

A reasonable strategy is to consider adrenalectomy in younger patients (<40 of age), those with low ACTH levels, and in cases of autonomous cortisol production – associated obesity, hypertension, diabetes mellitus and osteopenia. A patient with subclinical hypercortisolemia should receive glucocorticoid therapy peri- and post-operatively because of the risk of acute adrenal insufficiency. (1,14,15) Glucocorticoid therapy may last 6 to 18 months after unilateral adrenalectomy.(7)

Primary hyperaldosteronism: aldosterone – producing adenoma and adrenal nodular hyperplasia

Primary hyperaldosteronism is caused by aldosterone – producing adrenal masses, mostly by adenoma or nodular hyperplasia. Adrenal nodular (micronodular or macronodular) hyperplasia may involve one or both adrenal glands and is more frequent than aldosterone – producing adenoma. Primary hyperaldosteronism is the most common cause of secondary hypertension while approximately 1% of adrenal incidentalomas have proved to be aldosterone – producing adenomas. (1,9) Primary hyperaldosteronism should be suspected in the cases with early onset of hypertension, usually refractory to medication, and hypokalemia. However, these patients may have normal levels of potassium in the blood. The measurements of plasma aldosterone concentration (PAC) and plasma renin activity (PRA) are used to calculate PAC/PRA ratio (APR) which is the most commonly used test for screening of primary hyperaldosteronism. (16) The APR is most sensitive when blood is obtained 2h after waking up in the morning, in upright position, after a brief period of rest. An elevated PAC (>20 ng/dL) and a high APR (>30) are highly indicative for hyperaldosteronism. (9) However, the cut-off for a positive result may be laboratory dependent. Thus, PAC≥15 ng/dL and APR ≥20 have also been used as indicators for aldosterone – producing adrenal masses. (1) The interpretation of test results should be noted in caution in patients receiving some medications including antihypertensives, and whenever possible, such therapy should be discontinued prior to testing. (1,9) The negative suppression of aldosterone level after a salt challenge may be used as additional confirmatory test for primary hyperaldosteronism. (17)

When primary hyperaldosteronism is diagnosed it is important to determine the subtype of the disease. Patients with aldosterone – producing adenoma tend to be younger (<40 years old), have more severe hypertension and hypokalemia, and have higher PAC than those with adrenal nodular hyperplasia. However, there is no specific biochemical evaluation that reliably differentiates the subtype of primary hyperaldosteronism. (9) The proposed therapy for aldosterone – producing adenoma is surgical (in patients with unilateral source of aldosterone excess). However, preoperative adrenal vein sampling is mandatory for surgical decision if CT scan shows bilateral or no lesions (especially in patients over 40 years old) to exclude bilateral adrenal hyperplasia that is treated with selective and nonselective mineralocorticoid receptor blockers. (7,18)

Sex hormones-producing adenoma

Sex hormone – producing adrenocortical tumors are rare and typically occur in the presence of clinical manifestations of autonomous hormone secretion. Routine screening for excess androgens or estrogens in patients with adrenal incidentalomas is therefore not recommended. (1)

Clinically silent pheochromocytoma

Approximately 4 – 7% of AIs have proved to be clinically silent pheochromocytomas. (19) These tumors may be benign or malignant. Even when clinically silent this tumor can be lethal. (20) In approximately 25% of patients, pheochromocytoma is associated with familial syndromes (multiple endocrine neoplasia type 2, von Hippel-Lindau disease), thus genetic testing should be performed, especially in young patient. (7)

Radiological findings indicative for pheochromocytoma consist of increased attenuation on unenhanced CT, prominent vascularity of the mass, delayed washout of contrast medium, and high signal intensity on T2 – weighted MRI. (21) Biochemical assessment for pheochromocytoma is necessary in all patients with AI.

Measuring fractionated metanephrines and catecholamines in a 24 – hour urine are most widely used biochemical tests for diagnosis of pheochromocytoma. The additional measurement of fractionated catecholamines in the 24-hour urinary specimen is helpful in diagnosing dopamine – secreting pheochromocytoma. The measurement of plasma free metanephrines can also be used, but the value of this test is limited because of its low specificity. (22) The use of tricyclic antidepressants, decongestants, amphetamines, reserpine, and phenoxybenzamine should be discontinued to eliminate false – positive results. Surgical resection should be performed in all patients with pheochromocytoma and α-adrenergic blocking agent (phenoxybenzamine, doxazosin, or phenoxybenzamine/metyrosine) should be administered 1 to 3 weeks preoperatively. Long – term follow – up is advised because 10% to 15% of pheochromocytomas were found to be recurrent. (7)

PRIMARY ADRENOCORTICAL CARCINOMA

Primary adrenocortical carcinoma is a rare tumor with poor prognosis. The estimated prevalence of adrenal carcinoma in the general population is approximately 12 cases per 1 000 000. (23) Among the patients with adrenal incidentalomas, adrenocortical carcinoma was found in 4.7% of cases. (10) Although adrenocortical carcinoma can develop at any age, a bimodal age distribution was found, with the disease peaking before the age of 5 and in the 4th to 5th decade of life. (2) This tumor is functional in two thirds of cases: hypercortisolemia either alone or in association with virilisation is the most frequent presentation. Estrogen- and aldosterone- secreting adrenal carcinomas are rarely found. (8,24) The tumor size determines the risk of malignancy: adrenal cortical carcinoma accounts for 2% of AI up to 4 cm in size, 6% of tumors between 4.1 cm and 6 cm and 25% of tumors larger than 6 cm. (25) Imaging methods are helpful in differing between adrenocortical malignancy and benign lesions. Using CT, higher pre-contrast attenuation values (>10 Hounsfield Units) are usually obtained for malignant lesions because they generally contain less lipids in comparison to adrenal adenomas. After contrast administration, adrenocortical carcinomas present as inhomogeneous lesions with irregular borders and low percentage of contrast washout (<40%). MRI and CT have comparable accuracy in differentiation between benign and malignant adrenal lesions.

Adrenocortical carcinomas usually present as hypointense lesions on both MRI T1- and T2-weighted images with strong enhancement after contrast injection and delayed washout. (26, 27) Adrenocortical carcinoma can also be visualized by positron emission tomography (PET). Open adrenalectomy is the procedure of choice in the treatment of primary adrenocortical carcinoma.

Adrenal metastasis

Adrenal metastases account for 50 – 75% of all AI in patients with history of malignant disease. Adrenal metastases are bilateral in 10 – 15% of cases, they are usually larger than 3 cm and most frequently originate from primary tumors of the lung, breast, kidney, gastrointestinal tract, and melanoma or lymphoma. Adrenal hypofunction may occur due to tumor growth. In addition to imaging techniques, CT – guided fine – needle aspiration biopsy may be applied. Pheochromocytoma should always be excluded before fine – needle aspiration biopsy in order to avoid the potential hypertensive crisis. (8) If PET is performed, most malignant lesions will show avidity for [¹⁸F]-fluorodeoxyglucose. However, it is difficult to separate primary adrenocortical carcinoma from adrenal metastasis by using PET scan.

Follow-up of patients with AI

Any adrenal mass with concerning imaging characteristics and/or lesions ≥4 cm should be surgically removed because

of an increased risk of adrenal carcinoma. Follow – up of patients with adrenal incidentalomas involves assessment for growth and development of hormonal function.

The increase in size of a benign – appearing adrenal mass is used to screen for malignancy. Approximately 15% of AI increase in size during follow – up or may even shrink over time. There is no adrenal mass growth cut-off that can reliably confirm or exclude a malignant lesion. Patients with AI <4 cm and with radiologic characteristics consistent with benign lesions need to have imaging re-evaluation at 3 to 6 months and then annually for 1 to 2 years.(7) However, some recommend first scan within 6 months followed by annual CT for up to 4 – 5 years. Importantly, repeated CT scans increase the chance of causing fatal malignancy due to ionizing radiation. (8) If adrenal tumor grows (≥0.8 cm or ≥1 cm) and/or become hormonally active during follow – up, surgical removal should be considered. (28,7)

Hormonal evaluation should be performed at the time of diagnosis and then annually for up to 5 years. (7) The risk of hormonal progression was found to increase in the first 3 years and then remain stable. There is an opinion that hormonal follow – up in patients with non – functional AI ≤ 2 cm is probably of limited value because these lesions rarely progress in size or become functional. (8)

THE IMPACT OF ADRENAL INCIDENTALOMA ON CARDIOVASCULAR PATHOLOGY

Patients with adrenal incidentalomas have been reported to have an increased risk for cardiovascular diseases. (29) Accordingly, subtle cortisol production was found to be an independent risk factor for hypertension in patients with AI. (30) Moreover, patients with subclinical hypercortisolemia were found to have increased prevalence of adverse metabolic and cardiovascular outcomes. (31) Increased prevalence of insulin resistance, a major risk factor for cardiovascular events, has been reported in patients with functional AI. (32,33) Decreased insulin sensitivity was also reported in patients with nonfunctional AI. (34) Notably, patients with nonfunctional AI were found to have increased carotid intima media thickness. (35) and impaired cardiac morphology and function. (36) It has been suggested that some degree of adrenal autonomy that is not recognized by current methods, is responsible for increased cardiometabolic risk in patients with nonfunctional AI. (29) Accordingly, the level of *in vitro* steroid production was found to be similar in hormonally inactive adrenocortical tumors and subclinical hypercortisolism/overt Cushing syndrome suggesting cortisol autonomy in silent adrenal lesions. (37) Thus, increased prevalence of AI in patients with cardiovascular diseases is not only due to frequent use of imaging methods, but it is partly influenced by impact of AI on cardiovascular system.

CONCLUDING REMARKS

According to the AACE/AAES guidelines, all patients with adrenal incidentaloma should undergo clinical, biochemical, and imaging evaluation for hypercortisolism, aldosteronism (if hypertensive), the presence of a pheochromocytoma, or a malignant tumor. (7) Surgical removal should be applied in lesions ≥ 4 cm, pheochromocytoma, aldosterone producing – adenomas and unilateral nodular hyperplasia, cortisol – producing lesions with adverse clinical manifestations of hypersecretion, and in those with proved/suspected primary adrenocortical carcinoma. There is no definite recommendation for AI follow – up. Radiological reevaluation is advised in first 6 months, and then annually for 1 – 5 years. Hormonal screening should be done annually for 5 years. However, hormonal follow – up may be questioned for non – functioning AI which is ≤ 2 cm in size. Surgical removal should be considered in patients with tumor growth (≥ 0.8 cm or ≥ 1 cm) and/or *de novo* hormonal activity. After this review analysis several useful protocols could be made to help vascular surgeons to adequately treat patients with concomitant vascular disease and adrenal incidentalomas.

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