Chromogranin-A and adrenal incidentalomas: a role? which one?

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Summary

Adrenal incidentalomas are defined as asymptomatic adrenal masses occasionally discovered during high-resolution imaging procedures. The recommended case detection test is measurement of free plasma fractionated metanephrines. However, this test results in more false-positive tests than true positives, often leading to unnecessary tumor-localization attempts. Chromogranin A (CgA) is a member of the granin family contained in secretory vescicles of chromaffin adrenal cells. Serum CgA showed to be more accurate than urinary markers, including metanephrines, and was reported to be almost equivalent to the gold-standard plasma metanephrines assay by different authors. Because negative plasma fractionated metanephrines is highly predictive of the absence of pheochromocytoma, it is uncertain whether additional CgA testing should be added to the initial work-up. However, optimal test performance was achieved when the recommended, definitively diagnostic, 4-fold elevation criterion for plasma fractionated metanephrines was supplemented with serum CgA measurement for those cases with lesser plasma fractionated metanephrines elevations.

Key-words: **adrenal incidentaloma, pheochromocytoma, chromogranin A.**

Adrenal incidentalomas (AI) are defined as asymptomatic adrenal masses occasionally discovered during high-resolution imaging procedures as computed tomography (CT) or magnetic resonance (MR). AI, often benign, can secrete hormones and/or cathecholamines or not and their prevalence increases according to the CT and MR spatial resolution improvement. Phaeochromocytoma is a rare catecholamines-producing tumor derived from adrenomedullary chromaffin cells. Pheochromocytomas occur in up to 2–5% of patients with hypertension or adrenal incidentalomas, respectively. They are often considered in the differential diagnosis of severe or atypical hypertension and can prove fatal when diagnosis is delayed. Due to relatively unspecific symptoms, phaeochromocytoma is frequently detected during imaging procedures for non-adrenal disorders. Consequently, biochemical testing for phaeochromocytoma is indicated not only in symptomatic patients, but also in patients with AI as well as identified genetic predisposition[1]. The recommended case detection test, measurement of free plasma fractionated metanephrines, achieves 82–97% specificity with 96–99% sensitivity[2]. However, this level of specificity in a rare tumor results in more false-positive tests than true positives, often leading to unnecessary tumor-localization attempts. Strategies to reduce false positives have included the following:

1) retesting plasma fractionated metanephrines from asupine venipuncture setting or after removal of potentially interfering medications;
2) higher free plasma fractionated metanephrines diagnostic cutoffs;
3) additional tests, such as urine fractionated metanephrines or clonidine suppression; and 4) age-adjusted plasma fractionated metanephrine reference ranges[2].

Human chromogranin A (CgA) is a glycoprotein distributed in large dense core granules of neuroendocrine cells, particularly in adrenal medullary catecholamine storage vesicles. CGA is coreleased with amines/peptides from neuroendocrine tumor cells, and CgA levels correlate with

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tumor mass and secretory activity[3]. The reported sensitivity of CgA for detection of pheochromocytoma ranges from 65 to 100%[4-6]. Serum CgA showed to be more accurate than urinary markers, including metanephrines, and we recently demonstrated that serum CgA is equivalent to the gold-standard plasma metanephrines assay to detect/exclude pheochromocytoma among AI larger than 20 mm[7,8].

Recently, Algeciras-Schimnich and colleagues combined plasma fractionated metanephrine and CgA analysis and proved a 89% reduction in the number of false positives requiring further work-up[9]. Comparison of CgA and urine fractionated metanephrines as follow-up tests showed similar diagnostic efficiency. However, timed urine tests have a significant rate of inaccurate collections (~15%), and incorrect urine preservatives can lead to invalid results. CgA, in turn, can be secreted by nonchromaffin neuroendocrine tumors and can be elevated in liver or kidney failure or due to PPI therapy. As consequence some true-positive cases will therefore still be missed if a single follow-up test is used. This can be overcome by performing both CgA and urine fractionated metanephrine testing in a step-wise fashion and reviewing the results in the context of the clinical presentation[9]. Optimal test performance was achieved when the recommended, definitively diagnostic, 4-fold elevation criterion for plasma fractionated metanephrines was supplemented with both urine fractionated metanephrines and CgA analyses for those cases with lesser plasma fractionated metanephrines elevations. Because negative plasma fractionated metanephrines is highly predictive of the absence of pheochromocytoma, it is uncertain whether additional CgA or urine fractionated metanephrine testing should be added to the initial work-up.

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