SUPRARENAL INCIDENTALOMAS: HISTOLOGICAL HETEROGENEITY, MEASUREMENT OF DEHYDROEPIANDROSTERONE SULFATE AND RADIOCHOLESTEROL SCINTIGRAPHY IN THE DIAGNOSTIC WORK UP, AND FOLLOW UP OF THE INCIDENTALOMAS

Ph.D. Thesis

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1. Introduction

Incidentally detected adrenal tumors (incidentalomas) were first described about 20 years ago. Extended use of abdominal ultrasonography, computer tomography, and magnetic resonance imaging resulted in an increased prevalence of these tumors. Clinically inapparent adrenal masses are not a single pathological entity. After detecting an adrenal mass, further diagnostic strategy should be directed towards exclusion of metastasis into the adrenal gland, the primary malignancies being a rarity, and towards the detection of hormone excretion. Some of these tumors are cortical adenomas, and many of them produce steroid hormones. The glucocorticoid or mineralocorticoid excess caused by these tumors is usually mild, but may have clinical significance, as suggested by an increased prevalence of hypertension, diabetes, central obesity and hyperlipoproteinemia. Subclinical hypercortisolismus or subclinical autonomous glucocorticoid hypersecretion (SH) is defined as an autonomous cortisol secretion by an adrenal adenoma in patients without symptoms of Cushing’s syndrome. SH has not been adequately characterized. Dexamethasone suppression tests, 24-h urinary free cortisol, circadian rhythm of cortisol, ACTH, dynamic testing with CRH have all been proposed, but the gold standard for diagnosis of SH is still lacking. There are insufficient data regarding clinical usefulness of radiocholesterol scintigraphy and low
dehydroepiandrosterone sulfate level in the diagnostic work up of subclinical hypercortisolismus.

Objectives
1.1. Heterogeneity of adrenal incidentalomas

In our first article (Journal of Internal Medicine 1995) we report data on:
1.1.1.- pathological classification and tumor size
1.1.2.- hormonal activity of the incidentalomas
1.1.3.- follow up of primarily non-operated incidentaloma cases
1.1.4.- size and localization of the incidentalomas related to the histological dignity of the tumor.

1.2. Diagnostic value of DHEA-S

In the second article (Journal of Clinical Endocrinology and Metabolism 1996) we present data on dehydroepiandrosterone sulfate (DHEA-S) measurements in nonselected cases of suprarenal incidentalomas. We examined specificity, sensitivity and predictive value of a low dehydroepiandrosterone sulfate level for the benign nature, the cortical origin or the hormonal activity of adrenal incidentalomas.
1.3. Diagnostic value of adrenal scintigraphy
Third, we studied the diagnostic value of radiocholesterol scintigraphy and its correlation to subclinical hypercortisolism.

2. Subjects and methods

Subjects
2.1. Heterogeneity of adrenal incidentalomas
63 patients (38 female, 25 male) with suprarenal incidentaloma were included in this study. All patients were investigated by US (Hitachi EUB 40 or Acuson 128 XP/10) and CT (Hitachi CT W 400). In selected cases radiocholesterol scintigraphy was done. Oncological screening tests were performed in all patients. We examined hormonal activity of these tumors. Surgery was performed either if the tumor size was 30 mm or above, or if hormonal overproduction was present.

2.2. Diagnostic value of DHEA-S
84 nonselected cases of incidentally discovered adrenal masses were examined. For comparison 10 patients, suffering from metastatic carcinomatosis, without involvement of the adrenals were also investigated. To assess its differential diagnostic value, DHEA-S level was measured in all cases.
2.3. Diagnostic value of adrenal scintigraphy

Cortical radiocholesterol scintigraphy (11 MBq 75Se-6\(^{\text{a}}\)-selenomethylnorcholesterol) was performed in 41 patients with unilateral (n=33) or bilateral (n=8) suprarenal incidentalomas. In these cases CT indicated benign cortical adenoma. Screening laboratory tests for excess cortical hormone products were performed.

Methods

Hormone measurements:
- plasma ACTH was measured by RIA-CIS (Gif-Sur-Yvette, France)
- cortisol diurnal rhythm at 08.00 and 23.00-24.00
- overnight 1 mg dexamethasone suppression test
- plasma, urinary free cortisol by in-house \(^{3}\text{H}\) CPB methods, later by fluoroimmunoassay (Delfia, Wallac-OY, Turku, Finland)
- serum DHEA-S by RIA (Biomedicals INC, Costa Mesa, CA, USA)
- plasma renin activity (DuPont RIA) and serum aldosterone level (Serono RIA), later both measured by RIA (DiaSorin, S.R.L., Salugoa, Italy)
- 24 h urinary excretion of vanillylmandelic acid (in house chromatographic method and fluorimetric method)
- serum testosterone by a Hungarian Isotope Institute RIA
Statistical analysis:
- $\chi^2$ test
- standard methods for calculating sensitivity, specificity and predictive value were used to evaluate the diagnostic value of examined parameters.

3. Results

3.1. Heterogeneity of adrenal incidentalomas

3.1.1. Pathological classification of the histologically confirmed cases (n=31) proved significant histological heterogeneity of the tumors. In 10/31 cases, the pathological size was bigger than the CT size.

3.1.2. 20.6% of all incidentalomas and 61.5% of the 13 operated cortical adenomas showed subtle hormonal activity.

3.1.3. 27 incidentalomas <30 mm were followed-up 3-41 (mean 18) months and showed no growth in all but one case.

3.1.4. Sensitivity, specificity and predictive value (PV) of a tumor size >30 mm to indicate malignancy were 1.0, 0.56 and 0.27 respectively. The PV of a <30 mm tumor to exclude malignancy was 1.0. Incidentalomas were more common on the right than on the left side. There was no predominant right-or left-side localization of the primary malignant tumors or metastases.
3.2. Diagnostic value of DHEA-S
Of the 38 histologically confirmed cases, 6 of 12 patients with primary or metastatic malignant tumor of the adrenals and 7 of 14 patients with benign cortical adenoma had low DHEA-S levels. Thus, the sensitivity, specificity and predictive value of low DHEA-S level to indicate a benign adrenal tumor were 0.35, 0.50 and 0.60 and the values to indicate a cortical adenoma were 0.50, 0.67 and 0.47, respectively.
Of the 14 cases of histologically confirmed benign cortical adenoma, 10 had signs of hormonal activity, but DHEA-S was suppressed in only 7 cases. Thus, the sensitivity, specificity and predictive value of a low DHEA-S level to indicate clinically significant hormonal activity of a benign cortical adenoma were 0.60, 0.75 and 0.86, respectively. For comparison, 5 of 5 males and 2 of 5 females with metastatic carcinomatosis, but without involvement of the adrenals, also had low DHEA-S levels.

3.3. Diagnostic value of adrenal scintigraphy
3.3.1. Out of 33 patients with unilateral incidentaloma 11 had exclusive radiocholesterol uptake on the tumor site. 2/11 had subclinical hypercorticalismus diagnosed by other tests. Serum DHEA-S however, was low in these 2, and 6 additional cases (73%). A low DHEA-S was also found in 3/16 prevalent but not
exclusive isotope uptake and in only 1 out of 6 patients with simmetric or discordant uptake.

3.3.2. We detected good correlation of unilateral radiocholesterol uptake to low DHEA-S level (p=0.009).

4. Conclusions

4.1.1. Suprarenal incidentalomas are not a single pathological entity; they may be benign or malignant. The size of the tumors indicated by CT is often smaller than the pathological size.

4.1.2. Suprarenal incidentalomas often showe subtle hormonal activity. Cortical adenomas with subtle hormonal overproduction should be operated, irrespective of their size.

4.1.3. Tumors >30 mm should be operated, but smaller ones can be followed-up, they rarely show progressive growth.

4.1.4. Based on our results, tumor size <30 mm excludes malignancy.

4.2.1. In nonselected cases of suprarenal incidentaloma a supressed DHEA-S level is not a good predictor to detect a benign adrenal mass or cortical origin of the tumor.
4.2.2. In nonselected cases of adrenal incidentalomas a suppressed DHEA-S level is not a good predictor of hormonal activity. DHEA-S measurement may be valuable only after having ascertained the cortical origin and benign feature of the tumor.

4.3.1. Unilateral semiquantitative radiocholesterol uptake of an adrenal incidentaloma in combination with low serum DHEA-S concentration seems to be the most sensitive marker of subtle cortisol excess in the evaluation of suprarenal incidentalomas.

4.3.2. The combination of unilateral radiocholesterol uptake and low DHEA-S is strongly indicative of SH in adrenal incidentalomas.

4.3.3. Radiocholesterol scanning is a safe method to prove the cortical origin of suprarenal incidentaloma and should be used to exclude metastasis in selected patients with nonconclusive CT/MRI findings.
5. Publications


6. Abstracts

