

Adrenal Incidentalomas- Are We Over Investigating?

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Abstract

Adrenal incidentalomas are a relatively common cause of referrals to the endocrine department and the patient invariably ends up having the adrenal hormonal and further radiological work up in accordance to various guidelines. It is important to know whether clinicians are carrying out these tests in accordance to the evidence available. To answer this question we carried a 12 month retrospective study of patients who were referred to the endocrine department of our district general hospital. There were 37 patients referred out of which 28 were found to be non-secretory. 10 of the 16 normotensive normokalemic patients were inappropriately tested for aldosterone renin ratios. 1 patient was tested for DHEA level when there was no clinical suspicion of cancer or virilisation.

Conclusion: We over investigated about 1 in 3 patients with adrenal incidentalomas in terms of hormonal profile (aldosterone renin ratio). It is imperative that we investigate adrenal hormones in incidentaloma but at the same time we need to make right use of the resources and make rational decisions as to what tests are required, in accordance with the prevailing guidelines-usually the best evidence.

Keywords: Adrenal Incidentalomas; Aldosterone Renin Ratio

Introduction

Adrenal incidentalomas are any mass detected in the adrenal glands whilst being investigated for a different reason. It can occur in up to 4 - 5% of general population with the peak age incidence from 5th to 7th decade of life [1]. Various studies show that 75% of incidentalomas are non-secretory in nature and about 12% are cortisol secreting, 7% and 2.5% release catecholamine and aldosterone respectively. Only about 8% may have adrenocortical carcinoma and 5% may represent metastasis [1-3]. Any abnormal mass detected on the adrenal would essentially require to answer 3 questions- 1) Is it cancerous, 2) Is it producing anything autonomously and 3) Is it compressing any surrounding structures. In context of adrenal incidentalomas, first 2 questions are the most important ones. And to answer them, it is imperative to investigate further. More investigations means more economic burden but that has to be weighed against the benefits for the patient involved. In this era of evidence based medicine we tend to over investigate. The prevailing guidelines generally provide the best evidence in terms of investigations and treatment. However the recent guidelines for adrenal incidentalomas published in 2016 and 2017 do not answer all the questions, but that is the best current evidence to support the management of adrenal masses [4,5]. To answer the question as to whether we are over or under investigating these, we carried out this retrospective study looking at the referrals sent to our endocrine department with adrenal incidentalomas. Our hospital is not a tertiary centre but a district general hospital which is the first referral centre for the community.

Materials and Methods

We analysed all the referrals that were sent to the endocrine department over 12 months and separated the ones that were referred for adrenal lumps/masses/swelling/nodules. The clinic letters of these patients were then followed up till they were either discharged,

operated or lost to follow up. The primary outcomes were to see what investigations were done for the adrenal lumps, especially the hormonal workup. The secondary outcomes were to see what were the symptoms reported at 1st clinic visit and did the size of the lesion have any bearing on the final outcomes. The clinic letters and investigations were seen on the electronic medical records. Institutional Review Board approval or waiver was not sought for this study as it was a retrospective study looking at investigations that had already been done as well as this study did not involve any interventions.

Results

There were 37 patients referred with adrenal incidentalomas over a span of 1 year to our endocrine department at the district general hospital. 29 patients (78%) were in 5th to 7th decade of their lives. 76% (28 patients) were noted to be non-secretory in nature whilst only 3% (1 patient) had catecholamine secreting adenoma (Pheochromocytoma- histopathology proven and 4 cms in size) and another 3% (1 patient) had mixed Cortisol + catecholamine excess (4.8 cms in size, patient deceased due to a separate reason). 18% (7 patients) lost to follow up before any hormonal work up could be carried out. Hence only 30 patients data was referred for hormonal work up.

Age	Number of patients
4 th decade	2
5 th decade	9
6 th decade	11
7 th decade	9
8 th decade	6

Table 1: Age distribution.

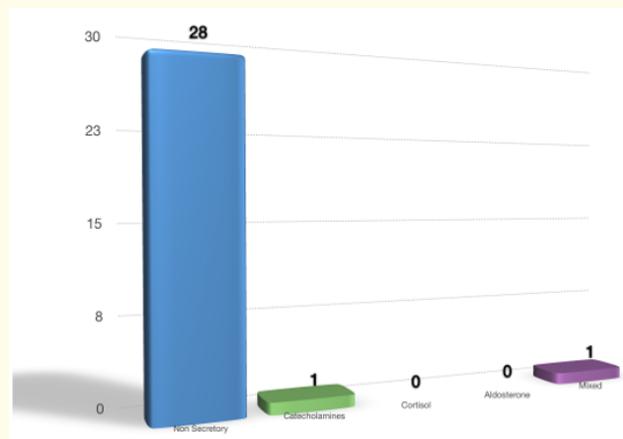


Figure 1: Hormonal work up of 30 patients.

Out of the 30 patients whose data was followed up, all but 1 had catecholamines tested, 28 patients had cortisol tested either by dexamethasone suppression test or 24 hour urine free cortisol while the remaining 2 had only 9 am cortisol tested. There were 16 normotensive normokalemic patients out of the 30 followed up ones (53%) and out of these 16, Aldosterone Renin Ratios were inappropriately tested in 10 of them. The rest of the 14 patients (47%) were hypertensive and had their aldosterone renin ratios were appropriately checked. 1 patient had his DHEA level checked despite no clinical or radiological evidence of excess sex hormone excess or any malignancy anywhere.

In terms of the size of the total number of patients referred with adrenal incidentalomas, 30 patients (81%) had size reported less than 3 cms, of which 6 had lost follow up, 1 was operated due to persistent indeterminate nature on scan and the rest 23 patients were finally discharged from the endocrine clinic as they were benign on the scan and non-secretory in nature. 4 of the 37 patients (11%) had the adrenal lesion size between 3 - 3.9 cms. 1 of these 4 patients was operated due to persistent indeterminate appearance on scans (histopathology was adenoma) and 1 lost follow up. The remaining 2 had benign appearance on CT adrenals and were non-functional on hormonal analysis, hence discharged. 3 patients out of 37 (8%) had adrenal incidentaloma size more than 3.9 cms - 1 had died due to a separate reason while the other 2 were operated - one of which was a pheochromocytoma. The deceased patient in this sub-group had mixed cortisol and catecholamine secretion.

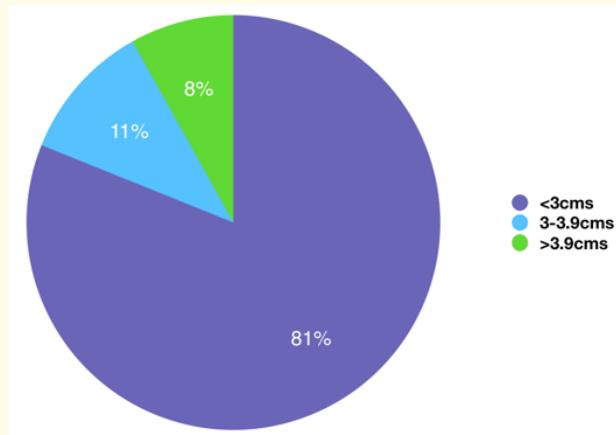


Figure 2: Adrenal size.

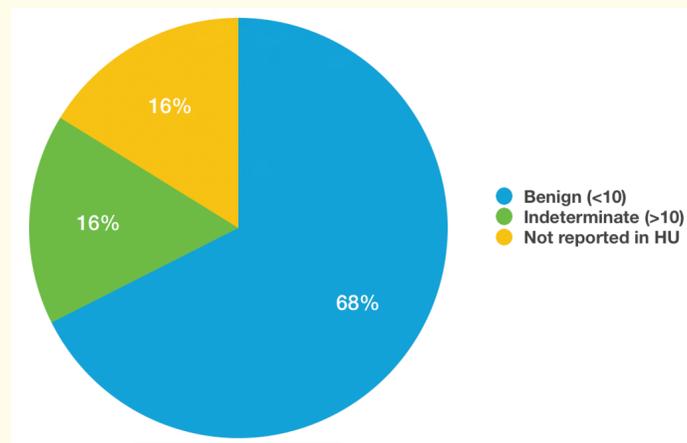


Figure 3: 1st CT Scan reporting.

In terms of outcomes in context of the initial CT scans reports, 68% (25 patients) had < 10 Hounsfield Units (HU) and none of them were secretory. 16% (6 patients) did not have any HU reports on the 1st scan out of which 1 was operated due its large size (13 cms) while in the rest of the 16% (6 patients) who had indeterminate densities (> 10 HU) on 1st scan, 2 had eventual benign washouts on adrenal dedicated CT scan, 3 were operated (1 pheochromocytoma, 2 persistently indeterminate and non-secretory and 1 had died due to separate reason who had mixed catecholamine + cortisol excess).

Finally in terms of the symptomatology, 81% (30 patients) did not report any symptoms on direct questioning and the rest 19% (7 patients) had mixture of symptoms from palpitations, sweating, flushing, weight gain and weight loss. 1 of the patients who reported sweating on direct questioning turned out to be a pheochromocytoma.

Discussion

This retrospective study presented us with some key points. The non-secretory nature and the age distribution was in hand with other studies [1-3] i.e. most of incidentalomas will be found in the later half of life and majority of them will be non-secretory. On the opposite side of the spectrum, there should be a lower threshold to aggressively investigate for malignancy and/or hormonal excess in a younger patient. The amount of initial investigations for the younger and older patients would be the same, the difference would be in the level of clinical suspicion for abnormalities and extended periods of follow up for younger patients. The European guidelines also suggest higher likelihood of malignancy in patients < 40 years of age and pregnancy [4]. Having said this, we have to appreciate that there will be a tendency to over investigate in the younger age group. But that has to be weighed against the clinical signs and symptoms as well as the possibility of a malignancy.

We had investigated the followed up patients for catecholamines, cortisol, aldosterone renin ratios and DHEA in all. The prevailing guidelines [4] recommended to test all the patients with adrenal incidentalomas for catecholamine and cortisol excess and to investigate for renin independent hyperaldosteronism if patient is hypokalemic or hypertensive. It also recommended to look for DHEA excess only if there is suspicion of adrenocortical cancer or virilisation. We under investigated 3 patients - 1 patient did not have catecholamine test while the other 2 only had 9 am cortisol done in place of overnight dexamethasone testing. The patient who did not have the catecholamines tested had benign washouts on CT adrenals and the responsible consultant did not feel it was appropriate to check the levels especially with the overall clinical scenario and symptomatology of that patient. The guidelines suggest to check for catecholamine excess for all the patients as there may be subclinical excess which would have implications on any future surgeries. We over investigated 10 normotensive normokalemic patients with aldosterone renin ratios. These were 10 patients out of 30 who got followed up for hormonal work up. We also ordered DHEA when it was not clinically indicated. The guidelines generally provide the best evidence surrounding the clinical condition and presents with recommendations accordingly. It is important to rationalise management within the available resources. The 11 extra investigations could have been avoided.

There was no size correlation seen in terms of surgical outcomes. There were patients operated in all the size sub-groups (< 3 cms, 3 - 3.9 cms and > 3.9 cms). The guidelines too do not recommend surgery solely on the size of the lesion but also mention that chance of a lesion being malignant is more if the size of the lesion is > 4 cms, hence should be for surgery [5] and in addition, we have to appreciate that the patient and the treating clinician would be anxious leaving any moderately sized mass in the body, irrespective of its secretory status, especially if patient is otherwise healthy. The only 2 patients who were secretory had their adrenal lesion size reported as 4 cms (catecholamine excess) and 4.8 cms (Mixed cortisol and catecholamine excess).

Adrenal CT density cutoff of < 10 HU for benign lesion appears reasonable based on a retrospective analysis of over 150 patients with adrenal masses who underwent both non-contrast CT and adrenalectomy [6]. Moreover, a consensus panel noted that a homogenous adrenal mass with smooth borders and a attenuation value of < 10 HU on a non-contrast CT is very likely to be a benign adenoma [7]. Majority of the referred patients to us had benign appearance on CT scan (< 10 HU) and all of them were non-secretory, however on the other side of the spectrum, the 2 patients who had secretory incidentalomas had indeterminate densities (> 10 HU). Studies have shown that radiological appearance of adrenal incidentalomas are independent of their secretory status [8,9]. The hormonal secretion could even happen in benign appearing lesions. Our small cohort had secretion from indeterminate appearing lumps.

Majority of the patients in this study did not have symptoms but surprisingly one of the patients who had sweating when asked on direct questioning as opposed to patient reporting it himself, turned out to be a pheochromocytoma. Previously it was thought that all pheochromocytomas are symptomatic but about 40% percent of pheochromocytomas may not have any symptoms [10]. Due to increased availability and widespread use of CT imaging, more pheochromocytomas are being picked up at an early stage, hence leading some clinicians to recommend measurement of plasma fractionated metanephrines in all patients of adrenal incidentalomas [11]. On the other

hand, a recent meta-analysis of signs and symptoms of pheochromocytoma [12], reported headache, sweating and palpitations as most common symptoms. However their individual presence had pooled sensitivity of only about 60%, 52% and 59% respectively, but when present together especially in presence of hypertension, it was much more weighted and informative (clinically) for diagnosis of pheochromocytoma, pending confirmation with laboratory and imaging. Our patient only had sweating which was not interfering with his activities of daily life hence thought not important to mention it whilst 1st clinic visit.

Conclusion

Majority of the patient that would be referred to endocrinology with adrenal incidentalomas would be benign and non-secretory. But in order to label it as benign non-secretory, we will have to investigate judiciously, importantly making sure that we do not miss out the functioning/cancerous lumps. At the same time we will have to use the hospital resources intelligently, so as not waste time and money ordering investigations that will not be helpful.

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