# Incidentaloma: from general practice to specific endocrine frame

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#### **Abstract**

Incidentaloma, a modern concept connected to technology progress, represents an accidentally discovered tumour, usually used for hypophysis and adrenals, and rarely for thyroid, parathyroids, and ovaries. This is a narrative review based on PubMed research, between 2012 and 2016 focusing on general and endocrine approach and current controversies. Main dilemma is the terminology itself: randomly imagery finding is enough or non-functioning profile and lowgrowth rate (not requiring surgery) should be mandatory? The controversies refers to best time framing of rescanning pituitary and adrenal incidentaloma and setting of clear criteria for subclinical Cushing's syndrome. The need for general practical guidelines is imperative so clinicians from different areas of medicine touse the same definition and protocols. Currently, the widely accepted part is represented by incidental finding. For restricted defined incidentaloma the best intervention is no intervention, while some cases may require surgery depending on tumours features, patient's age and preference.

**Keywords:** Pituitary, Adrenal, Incidentaloma.

#### Introduction

"Incidentaloma", a modern concept tight connected to recent technology progress, represents a term used to describe accidentally discovered tumours which are found during different medical investigations as ultrasound, computer tomography (CT), magnetic resonance imagery (MRI), etc.<sup>1,2</sup> These are performed by various practitioners from primary health care to specialists of secondary and tertiary centres.<sup>3-5</sup> The assessment is done either as a routine check-up or as an evaluation of a distinct condition that is not actually related to the incidentaloma.<sup>6-8</sup> The first step of approach

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is the random radiological finding and it is followed by running specific endocrine tests for each gland in order to highlight potential anomalies.<sup>2,9</sup> Even if any organ may associate a circumstantially revealed mass, the terminology of "incidentaloma" is commonly used for hypophyseal and adrenal glands and it is rarely applied for thyroid, parathyroids and ovaries.<sup>3,10,11</sup> Actually, there are two distinct meanings of "incidentaloma" issue: one comprises a large general area of any coincidental mass, regardless its size and endocrine profile (hyper- or hypofunction; benign or malign; solid, cyst or mix)while another restricts the topic to a specific endocrine context: only an occasionally discovered tumour associated with a clear non-functioning pattern and with a very low risk of further growing or malignant transformation and to which the best management is follow-up, not tumour removal<sup>2,6</sup> (Table). This last mentioned restrictive variant is more frequently used for pituitary and adrenals gland.<sup>6,12</sup> It has suggested that for pituitary incidentaloma usually the tumour is less than 1 centimetre (cm) diameter, while for adrenal less than 2cm (or 4 cm). Not all authors agree with this fact.6,12 Generally comprehensive area of incidentalomas does not involve any reference to tumours dimensions. 6,11,13 Another particular aspect is the thyroid that, due to the anatomical localisation, is accessible to palpation and so, large thyroid nodules which are previously unknown may be detected through direct physical examination.<sup>14</sup> The clinical evaluation followed by a specific radiological procedure to confirm it is not regarded as an incidental finding if local symptoms are already presented.14 Similarly, when clinical phenotype is suggestive for an endocrine condition and additional imagery tests are provided, the hormonally active tumours cannot be regarded as incidentaloma.<sup>6,9</sup> For instance, a short height of a child that is potentially related to hypercorticism needs supplementary investigations including a pituitary scan and finding an ACTH (Adrenocoticotropic Hormone) secreting tumour is not an incidentaloma.15 As age distribution pattern, adrenal and pituitary sites seem more frequent in elderly than in youth.<sup>9,16</sup> Most frequent adrenals are involved in the sixth and seventh decades.<sup>9,16</sup> A particular attention is needed to an adrenal mass in children and adolescence due to high malignancy risk.9,16 General approach of incidentalomas's management involves

**Table:** Endocrine incidentaloma: synthesis of main features (according to bibliographic references 1-35).

Site	Frequency*	Endocrine anomalies**	Frequency of using the terminology of incidentaloma	Most frequent underlining pathological report**	Radiological findings (type of imagery)	Cut-offs**	Context of discovery***
Pituitary	10-20%	Mild (functional) hyperprolactinemia	High	Pituitary microadenoma	Pituitary /cerebral CT, MRI	1 cm	Headache Eye field anomalies Neurological disturbances
Adrenal	5%	Subclinical hypercorticism	High	Corticoadrenal adenoma	Abdominal ultrasound, CT, MRI	2 (4)cm	Abdominal pain Kidney stones Urinary infections Oncologic protocol?
Thyroid	50%	Hyper/hypothyroidism Autoimmune thyroiditis	Low	Thyroid nodule either benign or malign	Neck (cervical anterior) ultrasound Cervical CT, MRI	any	Routine clinical exam # Breath, sleep,eating disturbances Oncologic protocol ?
Parathyroid	?	None	Low	Parathyroid adenoma	Neck ultrasound Cervical CT Cervical MRI	any	Similar with thyroid incidentaloma Plus: control of a priory known thyroid condition
Ovarian##	?	?	Low	Any	Pelvic ultrasound (abdominal or transvaginal probe) Pelvic CT Pelvic MRI	any	Pelvic pain Infertility

<sup>\*</sup>general use of the term "incidentaloma"

#thyroid is only endocrine gland (except for testes) which is palpable and needs to be checked to any routine endocrine physical evaluation but also during a general clinical examination ##ovarian site is rarely associated with the term incidentaloma thus limited data on endocrinology and gynaecological endocrinology are available ?oncologic protocol for a malignancy having a primary site un- related to the incidentaloma site.

multidisciplinary team. "True" incidentalomas need only serial imagery and endocrine work-up while large, hormonally active or potential malignant incidental findings are referred to neurosurgery, abdominal and thyroid surgery or gynaecology.<sup>4,11,16</sup>

## **Methods**

Our purpose is to introduce the main features of incidentalomas which connect different medical specialities to endocrinology as well as practical hormonal approaches and current controversies on the topic. This is a narrative review based on English literature Pub Med research, mainly using bibliographic references from 2012 to 2016.

# General Data Pituitary Incidentaloma (PI)

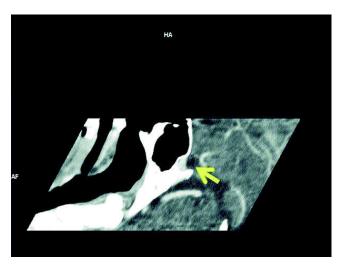
Pls are usually detected during investigations as CT or MRI, most frequently performed for headache(more than one third of cases) and other neurological or ophthalmic signs and/or symptoms<sup>2,10,12</sup> (Figure-1). The general prevalence of Pls varies from 10-20% of all patients who had a pituitary imagery done (only 1% of them have more

than 1cm diameter) and this increased during last decades due to more frequent usage and accessible imagery tools.5,7,8 The pathological entities that may be discovered as a PI are pituitary adenomas (most frequent) followed by Rathke's cleft cysts, meningiomas, craniopharyngiomas, different types of hypophysitis, etc, while strict endocrine parameters refers only to nonfunctioning hypophyseal microadenomas.5,8,10,12 When it comes to large extended area of PI, the required panel of investigations is mainly related to hypersecretion (most frequent secretion is of prolactin but IGF1 should be tested, too).5,12 Tumours larger than 1 cm or associating visual field anomalies need to be checked for hypopituitarism.<sup>2,5,12</sup> Screening tests for Cushing's syndrome are focused on subjects with metabolic complications and boneloss, knowing that, regardless of the site of injury (pituitary or adrenal), it is diagnosed in 1% of patients with high blood pressure and 5% of those with osteoporosis- related vertebral fractures.<sup>17,18</sup> PIassociated pituitary hypercortisolism has been reported with a 7.3% prevalence based on biochemical criteria. 17,18 Hormonally active tumours and those with local mass effects are initially referred to pituitary neurosurgery,

<sup>\*\*</sup>accepted for the restrictive endocrine use of the word "incidentaloma"

<sup>\*\*\*</sup>most probably unrelated to incidentaloma

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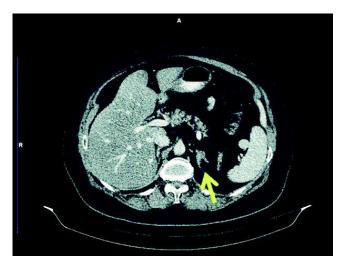


**Figure-1:** Pituitary incidentaloma. This is a 45-year old female who had a computer tomography performed for persistent headache. A pituitary microadenoma (0.4 x 0.44 cm) was found (reconstruction plane below) and remained stationary while follow-up for 5 years. Baseline prolactin level was of 6 ng/mL (normal values less than 20 ng/mL).

except prolactinomas which receive initial dopamine agonists; pituitary insufficiency should be replaced, too.<sup>2,5,12</sup> Pls, diagnosed as such using the restrictive connotation of the term, do not need any therapy, only serial follow-up since they have maximum 1 cm diameter, a clear non-secretor profile, and a non-significant risk of further increase.<sup>7</sup> The timing of repeating imagery is different from one country to another depending, mostly, on economical resources and specific regional protocols.<sup>7,12</sup> However, endocrine re-scanning is recommended annually for microadenomas and every 6 months for macroadenomas, and after first 3 years of unchanged dimensions, imagery should be spaced.<sup>5</sup> If an incidentally discovered tumour was referred to neurosurgery, first imagery should be done at least 3 months after; if no remnants are seen at MRI, the re-grow rate is for non-functioning adenomas of 13% and if a residual post-operative mass is found, the rate is 40%, thus annual MRI is needed within the next 5 years. 19

## Adrenal incidentaloma (AI)

Als have been found from 1% to 4-5% of subjects undergoing abdominal imagery, regardless of their size.<sup>6,9</sup> The classical routine which leads to an adrenal finding involves performing an abdominal ultrasound, CT or MRI for conditions as local pain, kidney and gallbladder stones, urinary infections, high blood pressure, hepatitis of any kind, previous cancer of non-adrenal site, etc.<sup>6,13</sup> (Figure-2). If we use the terminology of incidentaloma on general ground, the underlying diagnosis varies from cortico- and medulo-adrenal tumours, benign or malign, secretor or not, to adrenal metastases, myelolipomas,



**Figure-2:** Adrenal incidentaloma. This is 60-year old female, known with metabolic syndrome that had an abdominal ultrasound done. A left adrenal tumour (1.5 x 1.58 cm) was found and confirmed at computer tomography scan (transversal plane below) with stationary aspects for 2 years. Baseline morning plasma cortisol after 1 mg overnight Dexamethasone suppression test was 1.54  $\mu$ g/dL(normal levels below 1.8  $\mu$ g/dl).

cysts, etc.<sup>1,9,13</sup> When first approach an Al, a distinction between benign/malign behaviour is necessary using imagery clues.<sup>6,9</sup> The panel of investigations requires specific tests for pheochromocytoma, Cushing's syndrome in all patients, for primary hyperaldosteronism in hypertensive patients with and/or hypokaliaemia.<sup>6,9,13</sup> The management includes adrenalectomy, preferable by laparoscopic approach, for any secreting tumour, for non-secreting tumours larger than 4 cm and potentially malignant while hormonally inactive tumours smaller (especially those smaller than 2 cm which are true Al and fulfil the restrictive criteria of defining Al) should only be follow-up.<sup>6,9,13</sup> There are still dilemmas regarding the cost-effective protocols and strategies of endocrine work-up.<sup>1</sup>

# **Subclinical Hypercortisolaemia**

Subclinical Cushing's syndrome is an Al- related poorly described medical condition which recently has become the subject of many studies without a clear conclusion yet.6,20,21 The atypical phenotype, accounting for 5-20% of all Als, includes different cardio-metabolic complications as obesity, impaired glucose profile, high blood pressure, hyperlipidaemia, osteoporosis but lacking the full blown picture of classical Cushing's syndrome.<sup>22,23</sup> There are no standard criteria on this matter; some authors recommend its recognition based on screening suppression Dexamethasone test with a morning plasma cortisol level slightly above the normal limit of 1.8 μg/dL (≤50nmol/L), meaning a subtle anomaly of the hypothalamic-pituitary-adrenal axis, and the presence of

mild hypocorticism if the adrenal tumour is surgically removed.6,23,24 Most of the authors include persistent mild hypercotisolaemia in the general area of Al but controversies exist.6,20,21 Longitudinal and cross-sectional studies pointed that long-term persistence of subclinical phenotype as well as higher cortisol levels after 1 mg overnight inhibition Dexamethasone test is associated with an elevated risk of cardiovascular events and death when compared with clear non-secretor AI though other authors consider this entity rather harmless.<sup>20,22</sup> Another dilemma is the optimal management: follow-up the patient and treat the complications or adrenalectomy; currently, an individual decision is necessary based on complications, patient's age and option, the size changes of the tumour during periodic check-up, etc.<sup>23</sup> Local country protocols may point out the frequency of imagery scans while the presence of a full blown picture of unrelated endocrine condition may speed the discovery of an incidentaloma which may remain otherwise undiagnosed.<sup>25,26</sup>

## **Bilateral Adrenal Incidentalomas (BAI)**

A particular type of AI is represented by synchronous BAI. Case finding strategy on previously known genetic background as RET mutation on type 2A Multiple Endocrine Neoplasia does not represent an incidentaloma scenario but BAI may be found in other unknown conditions as congenital adrenal hyperplasia caused by CYP21A2 mutations.<sup>27</sup> Less than 1% of genetically tested patients had clear diagnosis while BAI do not predict the mutation; 17-hydroxyprogesterone assays may be used but with a low specificity.<sup>27</sup> Adrenal metastases, regardless uni- or bilateral lesions represents a delicate differential diagnosis of true AI; some discriminative imagery criteria are highly suggestive for malignancy like pre-contrast CT density of more than 20 Hounsfield Units.<sup>28</sup> The management of BAI is similar with unilateral Al and surgical removal should be done first on the largest tumour and then re-workup, considering a higher index of suspicion for subclinical phenotype of Cushing's syndrome.<sup>29,30</sup>

## Thyroid Incidentaloma (TI)

TI generally refers to a thyroid nodule (TN) which is very frequent in general population (up to half of people depending on series) so every physician including family physician may detect it.<sup>4,14,31</sup> But not any TN is a TI and several specific observations are necessary.<sup>4,14,31</sup> One is that in order to describe a nodule as TI no connection with breathing, eating, or local accuses (if they are presented)should be established.<sup>4</sup> Another is the fact that a routine neck ultrasound which is performed for nonendocrine reasons, for example, to check the carotid

artery flow may reveal a TN which, indeed, is a Tl.4 The other scenario is the incidental discovery of a TN during a CT, MRI, PET [18F] Fluoro-2-Deoxy-d-GlucosePositron Emission Tomography, PET CT, and other non-PET procedures done for oncologic purposes to evaluate the spreading of a non-thyroid cancer; TN is a TI if thyroid metastasis is ruled out.14,29,32,33 After discovery of TI, thyroid function needs to be first evaluated by assaying TSH (Thyroid Stimulating Hormone), eventually FreeT4 (Free Levothyroxin) and also autoimmunity profile by blood TPOAb (anti-thyreoperoxidase antibodies).14,34 Any function anomaly requires first medical treatment while euthyroidism status involves a fine needle aspiration if the minimum diameter of the TN is 1cm or if a highly suspect ultrasound pattern is identified.<sup>14,35</sup> Modern techniques of detection used on patients with a prior malignancy increased the ratio of TI discovery and controversies are still presented related to specific protocols for interpretation of accidental thyroid findings and for differentiation of a malignancy. 31,34,35

## Parathyroid Incidentaloma (PTI)

PTI is a very rare, less described topic that involves accidental finding of a parathyroid nodule, usually while performing a thyroid ultrasound (a prevalence of 1%) or Doppler ultrasound for neck vessels.<sup>3,36,37</sup> Calcium and parathormone should be assessed as screening; if hypercalcemia, bone or renal anomaly are already detected does not represent a PTI.3,36,37 A part from controversial definition of PTIs also relate to the management. Some suggest that PTI might represent a pre-clinical phase of primary hyperparathyroidismrelated adenoma or involve a "functional" or "true" adenoma and therefore it must be removed. According to the study criteria, functional PTI are found with a prevalence between 0.09% and 37.5%.36,37 When PTI is associated with normal calcium metabolism profile without clinical signs, an ultrasound follow-up is enough since the underlying pathological report is a non-active parathyroid adenoma.<sup>3,36,37</sup>

### **Ovarian Incidentaloma (OI)**

OI probably represents the least defined incidental finding, being situated at borderline between endocrinology and gynaecological endocrinology and oncological gynaecology.<sup>11</sup> Its discovery is accidental during any type of pelvic imagery; there is no specific endocrine definition for OI and thus it could associate with very different pathological diagnoses and high prevalence, especially in menopause (3 -18%).<sup>11</sup> Some lesions will require surgery especially if anomalies as testosterone level, CA-125 or ROMA score are found.<sup>11</sup>

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### Conclusion

Incidentalomas involve heterogeneous multidisciplinary field. Probably, the most important controversy in this field is the terminology itself: whether accidental discovery of a mass in an endocrine gland should be called incidentaloma or the term should be restricted. Other dilemmas refers to best time framing of re-scanning PI or AI and clear criteria for defining and treating subclinical Cushing's syndrome. The need for general practical guidelines is imperative so clinicians from different areas of medicine may use the same criteria of definition and similar protocols. Up to this moment, as the name itself shows, widely accepted part is represented by random discovery of a tumour. But after incidental imagery identification, further specific markers and investigations are necessary. Especially for PI and AI, the best intervention is no intervention while for the others, surgical approach, if needed, depends on tumour's features, patient's age and preference, changes that occur over time, etc.

# **Acknowledgement**

We thank the patients who gave us their written permission to use the images below.

Conflict of Interest: None.

Disclaimer: None.

Funding Disclosure: None.

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