Best Practice & Research Clinical Endocrinology & Metabolism 33 (2019) 101268

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

Management of pituitary incidentaloma

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ARTICLE INFO

Article history:
Available online 13 April 2019

Keywords:
incidentaloma
pituitary gland
apoplexy

Pituitary incidentalomas (PIs) represent a modern clinical entity increasingly recognized due to advances and easier accessibility to imaging techniques. By definition, PIs should be detected during brain imaging performed for investigation of a non-pituitary disease. Although anatomic variations, technical artefacts or pituitary hyperplasia might also be interpreted as PIs, the most relevant incidentally detected lesions are those that fulfill radiological criteria for a pituitary adenoma in asymptomatic patients or in the presence of subclinical diseases. The natural history of PIs is not fully determined, but there is a wealth of evidence indicating that most microincidentalomas (lesions < 10 mm) have a benign course, whereas macroincidentalomas (≥10 mm) deserve more attention due to an increased risk for hormone abnormalities and mass effects. This concept is important to keep in mind for an optimal diagnostic and therapeutic management of PIs that avoids harmful iatrogenesis and unnecessary health care costs.

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https://doi.org/10.1016/j.beem.2019.04.002
1521-690X/

Introduction

Pituitary incidentalomas (PIs) can be defined as unexpected abnormalities of pituitary or non-pituitary origin detected during brain imaging performed for unrelated indications. They are classified in micro (<10 mm or 1 cm) or macroincidentalomas (≥10 mm or 1 cm) according to their size. In most cases, PIs are detected by computed tomography (CT) or magnetic resonance imaging (MRI) during evaluation of non-specific neurological symptoms, headaches or head trauma [1]. Nevertheless, the definition of PIs is not necessarily as straightforward as it appears [2,3]. In some studies, only lesions that fulfill imaging criteria for a pituitary adenoma are considered as PIs [4,5], while in other series there is no such distinction, and even technical artefacts or physiological pituitary enlargement are included in the definition [6–8]. It is also clear that not all detected lesions are true PIs, as some signs and symptoms that are not readily linked to a pituitary disease are only recognized late in the diagnostic workup [9,10].

Differences in the definition of PIs and the type of technique employed in imaging studies are the main factors affecting their prevalence. In retrospective MRI studies carried out in unselected individuals, the rate of microincidentalomas varies from 10 to 38%, while the percentages of macroincidentalomas are much lower, varying from 0.16 to 0.3% [8]. These numbers have a fairly good degree of correspondence with that seen in post-mortem studies. An analysis of 32 autopsy series revealed 2023 adenomas in 18,902 pituitaries, resulting in a mean prevalence of 10.7%, with frequency of identified PIs ranging from 1.5 to 31% among the 32 studies [11]. Noteworthy, only 7 (0.34%) macroincidentalomas were identified, suggesting that most pituitary macroadenomas probably come to clinical attention at some point in life [7,11]. Accordingly, pituitary macroadenomas are commonly seen in the clinical practice, distributed equally in adult men and women throughout all age groups, and in many cases, they are erroneously interpreted as incidentalomas [7,9,11–13].

Although the natural history of PIs is not fully established, the findings from both imaging and post-mortem studies indicate that an incidentally discovered pituitary microadenoma rarely transforms into a pituitary macroadenoma [8–10]. As intuitively expected, solid lesions and macroadenomas have a greater tendency for growth over the years than cystic lesions and microadenomas, with visual deterioration occurring almost exclusively in macroadenomas and pituitary apoplexy rarely seen in observational studies [5,6,9,13–15]. Immunohistochemistry of PIs found at autopsies has shown that roughly two-thirds of incidentally detected pituitary adenomas are apparently null cells tumors or stained for prolactin [16].

Neuroradiological differential diagnosis

When a pituitary lesion is incidentally disclosed by a head imaging examination, the differential diagnosis includes virtually all tumorous and nontumorous diseases that can be found in the sellar and perisellar regions [17]. By far, pituitary adenomas are the most common cause of PIs, accounting for 70–80% of the cases in neuroradiological and surgical cohorts, followed by Rathke's cleft cysts and craniopharyngiomas [18,19]. This contrasts with the findings of a postmortem Japanese study, where Rathke's cleft cysts were first in place and pituitary adenomas second, followed by a combination of nodular hyperplasias, infarctions, hemorrhages, granular cell myoblastoma and lymphocyte infiltration [20].

MRI focused to hypophysis is the imaging technique of choice and should be analyzed by an experienced radiologist. The exam includes pre and post-contrast T1-weighted and T2-weighted spin-echo coronal and sagittal sections with thin slices. CT can be complementary in the evaluation of the bone structure of the sella and presence of calcifications. It is important to exclude imaging artefacts that can be inappropriately described as PI, such as normal anatomical variations, partial volume artifacts that occur when parts of different structures are included in the same slice (for instance, anterior pituitary gland, intracavernous carotid arteries, sphenoid sinus and dorsum sellae), vascular abnormalities (persistence of intrasellar trigeminal artery) or magnetic susceptibility causing imaging distortions due to different signal intensities from adenohypophysis and bone [8,21].

Pituitary hyperplasia (PH) is another entity that can be misinterpreted as a PI. A French study described 7 women with PH aged 15–27 years, with normal pituitary function, who were referred due to an initial radiological suspicion of a pituitary tumor. Two of them were initially seen by a neurosurgeon and underwent transsphenoidal surgery (TSS). During a follow-up period varying from 2 to 8

years, MRI showed stable pituitary size [22]. PH can be present during adolescence, menopause, pregnancy, and also in primary hypothyroidism, sometimes displacing the optic chiasm. Radiological findings that are clues for PH include symmetrical pituitary enlargement, superior convexity, normal adeno and neurohypophysis signals and homogenous contrast enhancement [8,22] (Fig. 1). The diagnosis of PH is extremely important to avoid extensive hormonal and MRI surveillance and unnecessary and potentially harmful surgery. Noteworthy, these cases do not reflect pituitary lesions and should not be addressed with the same recommendations as for PIs.

The pitfalls of neuroimaging can be further exemplified by a classical study designed to determine the prevalence of focal lesions larger than 3 mm suggestive of pituitary adenoma in 100 asymptomatic volunteers. MRI scans were interpreted by 3 independent neuroradiologists, and a "pituitary adenoma" was diagnosed in 34, 10 or 2 participants, depending upon the agreement on the diagnosis between 1, 2 or 3 of them [23]. This finding emphasizes the importance of evaluating radiological data within an appropriate clinical context.

Clinical approach

Initial evaluation

A careful anamnesis and physical examination, looking for primarily unsuspected signals or symptoms of pituitary hyper or hypofunction and subtle neuroophthalmological complaints, are essential part of the initial evaluation of a patient with either a micro or a macro PI. In lesions reaching optic chiasm, a visual evaluation is mandatory, including Goldman perimetry, even in patients with no visual complaints, and examination of III, IV and VI cranial nerves, in cases with cavernous sinus invasion should also be performed [24].

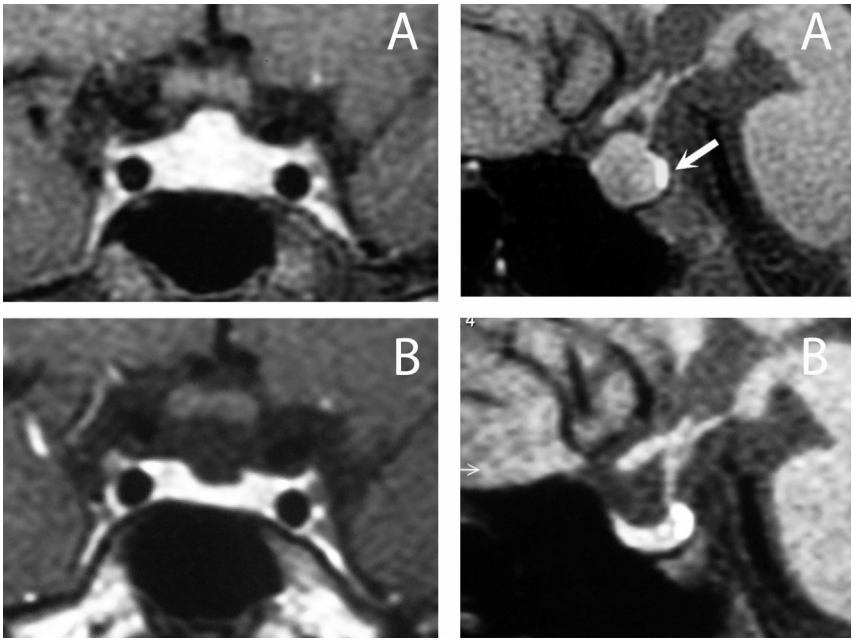

Fig. 1. Magnetic resonance findings in a case of pituitary hyperplasia due to primary hypothyroidism. The patient was an 8 years-old girl who presented with headache. Initial radiological diagnosis was "pituitary macroadenoma". Panels A (at baseline): coronal T1-weighted postcontrast (*left*) and sagittal (*right*) imagens show a symmetrical pituitary enlargement with a central superior convexity, homogenous contrast enhancement and the presence of neurohypophysis signal (*arrow*); Panels B (after 6 months of therapy with levothyroxine): coronal (*left*) and sagittal (*right*) imagens without abnormalities.

The Endocrine Society Clinical Practice Guideline recommends that all patients with a PI, regardless of its size, should undergo laboratory evaluations for hypopituitarism and for pituitary hypersecretion. The document emphasizes, however, that the recommendations relied heavily on clinical experience, as literature on this topic is sparse [2]. Not surprisingly, there are different opinions on how to screen for TSH, ACTH, GH and FSH/LH deficiencies, but as a general rule, the investigation includes measurements of total or free T4, TSH, cortisol, IGF-I, LH and FSH in men and postmenopausal women, and total testosterone in men. Stimulation tests should be undertaken for ACTH and GH deficiency when baseline results are not confirmatory [2,25]. This approach is clearly justified in all macroincidentalomas, since at least one pituitary axis is compromised in 60–85% of the cases [26]. Nevertheless, the hormone investigation in microincidentalomas is much more controversial [2,11]. In one study involving 38 patients with non-functioning microadenomas, half of the patients with normal IGF-I levels had insufficient GH response to GHRH-arginine stimulation test [27]. However, the patients who failed the test had a mean BMI of 36 kg/m^2, significantly higher than those who passed the test and healthy controls, and thus the test results could represent functional GHD due to obesity instead of a true GHD due to the microadenoma. In the same study, TSH, FSH/LH and ACTH deficiencies were observed in 15, 10 and 1 patient, respectively [27]. Another large retrospective cohort of non-functioning pituitary adenomas (NFPA) found at least one pituitary deficiency at diagnosis in 33.3% of microadenomas, independently of tumor localization within the sellar region [28]. On the other hand, other studies have failed to identify pituitary deficiencies in microincidentalomas [4,9,14,29,30], leading some authors to advocate against the investigation for hypopituitarism in these cases [24,26,29,30]. The discrepant results are likely related to different tests and criteria used to diagnose pituitary deficiencies, false positive results, and the underlying pathological conditions.

Similarly, the investigation of subclinical PRL, GH, and ACTH hypersecretion in all PIs has also been a matter of debate, especially in microadenomas. King and colleagues performed a cost-effectiveness study and concluded that in an incidental asymptomatic pituitary microadenoma, a single PRL test may be the most cost effective management strategy [31]. This is agreement with a metaanalysis of 7 postmortem studies in which immunohistochemical staining was positive for PRL in 25–41% of tumor specimens, but only rare cases were positive for GH or ACTH [32]. In contrast, pituitary hypercortisolism was diagnosed by biochemical criteria in five (7.3%) patients with PIs (histologically confirmed in 4.4%, three micro and two macroadenomas), leading the authors to conclude that subclinical or mild hypercortisolism may be more common than generally perceived in patients with PIs [33]. Nevertheless, a careful analysis of these cases revealed that the patients had several signs and symptoms and not all identified tumors were true PIs. There have been also case reports of clinically silent GH-expressing adenomas without any signs or symptoms of acromegaly but with elevated IGF-I and GH levels, especially presenting as macroincidentalomas [29,34,35]. Mild elevation of IGF-I levels in asymptomatic patients with PIs should be interpreted with caution as 2.5% of normal individuals present IGF-I levels above the upper limit of the reference range [36]. Moreover, it is worth to mention that the natural history and optimal approach in patients with early diagnosis of asymptomatic Cushing's disease and acromegaly still need to be determined [37,38], despite most experts would recommend surgical removal of the adenoma in these cases [39]. Undoubtedly, there is no need to test for pituitary hormone excess when the imaging suggests Rathke's cyst, craniopharyngiomas or any lesion clearly unrelated to a pituitary adenoma.

Follow-up

Observation versus surgery or medical therapy

As previously mentioned, after exclusion of other unrelated lesions, PIs can be divided after the initial hormonal screening in different pituitary adenomas subtypes [2]. This definition will directly impact on the management of these tumors. Functioning tumors almost always require treatment, while for NFPA some factors like age, presence of compressive symptoms and proximity of the optic pathways should be considered to define the best approach (surgery vs observation) [40].

The primary treatment of macroprolactinomas and symptomatic microprolactinomas is medical therapy with dopamine agonists. In the case of an asymptomatic hyperprolactinemic patient with an incidentally detected microadenoma, treatment is not required and the use of concomitant PRL-induced drugs or other causes of increased PRL levels should be investigated [30,41,42]. Moreover, when serum PRL levels are below 250 ng/mL in the presence of macroincidentaloma, it is important to distinguish between a true macroprolactinoma and a stalk mass effect due to another type of tumor [42]. When treatment is indicated, cabergoline is the drug of choice in most prolactinomas due to its higher efficacy and better tolerability in comparison with bromocriptine [43]. In women with a pregnancy desire, bromocriptine may be preferred due to the larger amount of data in the literature regarding its safety in pregnancy [41].

TSS is recommended as the treatment of choice for pituitary incidentalomas that ultimately are diagnosed as corticotropinomas or somatotropinomas after the hormonal evaluation [2]. The exceptions are patients with high surgical risk, who refuse surgery or with unresectable tumors (virtually all adenoma inside the cavernous sinus). If surgery is contraindicated in a somatotropinoma diagnosed as PI, treatment with first-generation somatostatin receptor ligands (octreotide or lanreotide) can be considered [44], whereas in corticotropinomas, main alternative therapeutic options in patients with subclinical hypercortisolism are pituitary-directed medical therapy (pasireotide or cabergoline) or steroidogenesis inhibitors (ketoconazole or metyrapone) [45].

The majority of PIs are NFPA that can be managed only with observation and follow-up with a second MRI after 6 or 12 months, depending on tumor size and invasiveness [9–15,24,29–31,39,40]. Less than 5% of microincidentalomas increase in size exceeding 10 mm, while growth of macroincidentalomas has been observed in up to 40% of patients followed for 8 years [40]. According to the Endocrine Society guidelines, if the tumor does not grow in the second MRI, imaging should be repeated every year for macroincidentalomas and every 2 years in microincidentalomas for the following 3 years, and gradually less frequently thereafter [2].

The absolute surgical indication is the presence of neuroophthalmological symptoms, especially visual loss, most frequently bitemporal hemianopsia [2,40]. In those patients with tumors that abut the optic chiasm but do not present visual abnormalities, surgery can also be indicated, especially in younger patients who are at higher lifetime probability of tumor enlargement and consequent visual disturbance. Also, in women who plan to become pregnant and have tumors that are close to the optic chiasm, the risks (especially hypogonadism) and benefits (potentially harmful mass effect facilitated by pregnancy-related lactotroph hyperplasia) of surgery should be considered and discussed with the patient [2,40]. Although some studies have demonstrated beneficial effects of dopamine agonists in NFPA [46–48], medical therapy of these tumors remains a very controversial issue and the “wait and see” approach is still preferable in most cases [2,8,10].

In those NFPA where observation was the initial choice, surgery can be indicated in case of progressive growth, especially if clinically significant and in the direction of the optic chiasm [2,40]. Surgical indication due to progressive loss of pituitary function in the follow-up is a more controversial issue, since many patients do not recover pituitary function after surgery and can even develop new pituitary axis deficits [49]. Nevertheless, some centers and guidelines suggest TSS as an option in this situation [2,40]. The consensus document of the French Endocrine Society also indicates surgery in two other situations: for non-compliant patients with a high risk to lose follow-up and in suspected cases of malignancy (although these lesions are rarely asymptomatic) [40]. Table 1 summarizes the main indications for surgical treatment of PIs.

Risk of apoplexy

Pituitary apoplexy is defined as an acute event characterized by hemorrhage or infarction of an adenoma that can lead to compressive symptoms due to the rapid volume expansion, being a life-threatening situation in some cases. The most common symptoms are headache, ophthalmoplegia and acute visual loss [50]. Therefore, it is a concern in patients harboring macroincidentalomas whose initial management involves only serial observation.

Despite the theoretical risk, the majority of studies show that pituitary incidentalomas present a very low risk of apoplexy, as previously mentioned [2,5,6,9–15]. A systematic review and metaanalysis

Table 1
Indications for surgical treatment in incidentally detected pituitary adenomas.

Degree of recommendation	Indications
Absolute indication	*At initial evaluation*
	Non-functioning pituitary adenoma with compressive symptoms (especially visual loss)
	If proven to be an ACTH-secreting adenoma (Cushing's disease)
	If proven to be a GH-secreting adenoma (most cases of acromegaly)
	During follow-up
	Non-functioning pituitary adenoma presenting a significant growth (especially if toward the optic chiasm)
	Apoplexy (in macroadenomas if associated with compressive symptoms)
Relative indication	*At initial evaluation*
	Asymptomatic non-functioning pituitary adenoma abutting the optic chiasm (especially in young patients)
	Non-functioning pituitary adenoma close to the optic chiasm in women with a desire for pregnancy
	Non-functioning macroadenomas with high risk of apoplexy (ex: patients in use of anticoagulants)
	Non-functioning macroadenomas in non-compliant patients with a high risk to lose follow-up
	Suspected cases of malignancy (which are rarely asymptomatic)

of the literature including studies published until 2011 found an incidence of apoplexy of only 0.2% of patients/year, increasing to 1.1% when including only macroincidentalomas [15]. Recently, no case of apoplexy was observed in a series of 190 pituitary incidentalomas followed for a median period of 5 years, in contrast with a rate of 8.5% after a median follow-up of 5.7 years in 410 clinically manifesting pituitary adenomas [1]. The risk of apoplexy is, however, potentially higher in patients with macroincidentalomas presenting predisposing factors, like the concomitant use of anticoagulant therapy and in this situation, surgery should be considered, especially in tumors that are close to the optic chiasm [40]. Thus, although rare, clinicians should be aware of signs and symptoms of apoplexy to avoid delays in its diagnosis and treatment [50].

Personal experience and conclusions

The lack of clear definition of PIs and the paucity of long-term prospective studies on their natural history has resulted in different opinions about their optimal management. In Fig. 2, we present a practical approach according to our personal experience, which is based on the premise that a true PI is not associated with any signal and symptom directly related to it, either at an initial evaluation or retrospectively after its detection by imaging. In this clinical context, the next step is to assess the size and nature of the lesion, separating those incidental findings that represent anatomical variations, artifacts, PH, or any other lesion unrelated to pituitary adenomas.

In our view, no hormonal evaluation is required for cystic microincidentalomas and solid lesions smaller than 5 mm. For solid microincidentalomas measuring 5–9 mm, we favor a simple and cost-effective investigation with measurements of PRL and IGF-I. If hormone levels are high in a completely asymptomatic patient, a careful analysis of false positive results should be performed and a "wait and see" approach might be an option [36,38,41]. Medical treatment for PRL-secreting adenomas or surgery for GH-secreting adenomas can be considered at any time if the patient becomes symptomatic or tumor grows during follow-up. When hormone levels are normal, yearly MRI is recommended in the first two years, with surgery been indicated if a significant and threatening tumor growth occurs. Otherwise, if the tumor remains stable, the patient can be followed clinically thereafter.

In macroadenomas, we perform a complete evaluation of the pituitary function with measurements of free T4, TSH, IGF-I, PRL, cortisol, FSH/LH, and testosterone in men, and stimulations tests for GH and ACTH deficiencies, when basal serum levels of IGF-I and cortisol are inconclusive. Visual campimetry is required when the macroadenoma expands towards the optic chiasm [2,40]. In functioning macroadenomas, treatment is always indicated, either pharmacological or surgical depending on the type of

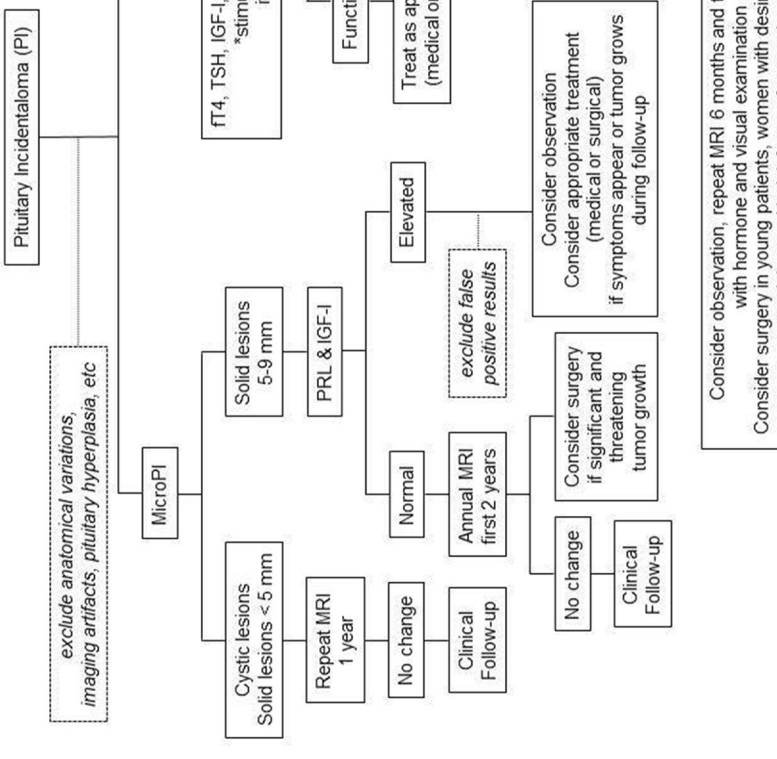

Fig. 2. Approach of a pituitary incidentaloma (PI) in completely asymptomatic patients.

tumor [41,44,45]. In NFPA without mass effect, an expectant management can be adopted with annual follow-up with imaging and pituitary function, with surgical indication in case of significant tumor growth. In NFPA with a potential mass effect on the optic pathways or causing unsuspected hypopituitarism, we always indicate surgery in the presence of visual abnormalities. If visual campimetry is normal, the "wait and see" approach can be considered, with repeated MRI after 6 months and then yearly, associated with hormone and visual examinations. In particular circumstances, like young patients, women with desire for gestation and those with risk factors for apoplexy (such as anticoagulants use), we recommend surgery even without visual abnormalities. When surgery is indicated, it is essential to take into account the availability of a multidisciplinary reference center in pituitary disease management with an experienced neurosurgery team for optimal success rates [51].

Conflicts of interest

The authors have no conflict of interest to declare.

Role of the funding source

There are no sources of funding related to this article.

Practice points

- Many PIs seen in clinical practice refer to anatomical variations, technical artifacts and lesions smaller than 5 mm that do not need any further investigation
- A true PI should not be associated with any signal and symptom directly related to it, either at an initial evaluation or retrospectively after its detection by imaging
- Most microincidentalomas have a benign course and do not need an extensive and prolonged diagnostic workup
- Observation is the appropriate initial therapeutic approach for non-functioning macroincidentalomas that do not cause mass effects
- Surgery is mainly indicated in patients with visual abnormalities or at high risk of developing visual loss or apoplexy during follow-up

Research agenda

- Need for more prospective long-term studies evaluating the natural history of PIs
- More homogeneous and clear definition of PIs among the studies, avoiding the inclusion of patients who do not represent true PIs

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