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Consensus

Management of nonfunctioning pituitary incidentaloma☆

Prise en charge des incidentalomes hypophysaires non fonctionnels

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Abstract

Prevalence of pituitary incidentaloma is variable: between 1.4% and 27% at autopsy, and between 3.7% and 37% on imaging. Pituitary microincidentalomas (serendipitously discovered adenoma < 1 cm in diameter) may increase in size, but only 5% exceed 10 mm. Pituitary macroincidentalomas (serendipitously discovered adenoma > 1 cm in diameter) show increased size in 20–24% and 34–40% of cases at respectively 4 and 8 years' follow-up. Radiologic differential diagnosis requires MRI centered on the pituitary gland. Initial assessment of nonfunctioning (NF) microincidentaloma is firstly clinical, the endocrinologist looking for signs of hypersecretion (signs of hyperprolactinemia, acromegaly or Cushing's syndrome), followed up by systematic prolactin and IGF-1 assay. Initial assessment of NF macroincidentaloma is clinical, the endocrinologist looking for signs of hormonal hypersecretion or hypopituitarism, followed up by hormonal assay to screen for hypersecretion or hormonal deficiency and by ophthalmologic assessment (visual acuity and visual field) if and only if the lesion is near the optic chiasm (OC). NF microincidentaloma of less than 5 mm requires no surveillance; those of ≥ 5 mm are not operated on but rather monitored on MRI at 6 months and then 2 years. Macroincidentaloma remote from the OC is monitored on MRI at 1 year, with hormonal exploration (for anterior pituitary deficiency), then every 2 years. When macroincidentaloma located near the OC is managed by surveillance rather than surgery, MRI is recommended at 6 months, with hormonal and visual exploration, then annual MRI and hormonal and visual assessment every 6 months. Surgery is indicated in the following cases: evolutive NF microincidentaloma, NF macroincidentaloma associated with hypopituitarism or showing progression, incidentaloma compressing the OC, possible malignancy, non-compliant patient, pregnancy desired in the short-term, or context at risk of apoplexy.

Keywords: Nonfunctioning pituitary incidentaloma; Microadenoma; Macroadenoma

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☆ Consensus of the French Endocrine Society: nonfunctioning pituitary adenoma.

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Résumé

La prévalence des incidentalomes hypophysaires est variable : 1,4 à 27 % à l'autopsie; 3,7 à 37 % en imagerie. Les microincidentalomes hypophysaires (adénomes de découverte fortuite de moins d'un centimètre de diamètre) peuvent augmenter de taille, mais moins de 5 % d'entre eux dépassent 10 mm. Les macroincidentalomes hypophysaires (adénomes de découverte fortuite de plus d'un centimètre de diamètre) augmentent de taille dans 20–24 % ou 34–40 % des cas si la durée de suivi est respectivement de 4 ans ou 8 ans. Le diagnostic différentiel radiologique nécessite une IRM centrée sur l'hypophyse. L'évaluation initiale d'un microincidentalome non fonctionnel (NF) est d'abord clinique, à la recherche, par un endocrinologue, de signes d'hypersecrétion (signes d'hyperprolactinémie, d'acromégalie ou syndrome de Cushing), complété par un dosage systématique de prolactine et d'IGF-1. L'évaluation initiale d'un macroincidentalome NF est clinique, à la recherche, par un endocrinologue, d'une hypersécrétion hormonale ou d'une insuffisance antéhypophysaire (IAH), complétée par des dosages hormonaux à la recherche d'une hypersécrétion ou d'un déficit hormonal et par une évaluation ophtalmologique (acuité visuelle et champ visuel) si et seulement si la lésion est à proximité ou au contact du chiasma optique (CO). Les microincidentalomes NF de moins de 5 mm ne relèvent d'aucune surveillance. Les microincidentalomes NF de diamètre ≥ 5 mm ne sont pas opérés mais surveillés au moyen d'une IRM réalisée à 6 mois puis à 2 ans. Les macroincidentalomes situés à distance du chiasma sont surveillés par une IRM à 1 an et une exploration hormonale (recherchant une IAH), puis tous les 2 ans. Pour les macroincidentalomes situés à proximité du chiasma, s'il est décidé de les surveiller et de ne pas les opérer, une IRM est recommandée à 6 mois avec explorations hormonale et visuelle, puis tous les ans pour l'IRM et le bilan hormonal, et tous les 6 mois pour l'évaluation visuelle. Le traitement chirurgical est recommandé dans les situations suivantes : microincidentalomes NF évolutifs, macroincidentalomes NF avec IAH, ou évolutif, lésion comprimant le chiasma optique, doute sur une lésion maligne, patient non observant, grossesse souhaitée à court terme, contexte favorisant une apoplexie.

Mots clés : Incidentalome hypophysaire non fonctionnel ; Microadénome ; Macroadénome

Pituitary incidentaloma is a pituitary lesion serendipitously discovered on brain imaging (CT, MRI or PET) performed for some other reason. The present consensus conference on non-functioning (NF) pituitary adenoma does not seek to address the entire issue of pituitary incidentaloma, but focuses on diagnosis and treatment of clinical nonfunctioning serendipitously discovered adenoma.

1. Epidemiology

The epidemiology of pituitary incidentaloma is founded on a few mainly retrospective studies. Frequency, assimilated to that of NF pituitary adenoma, is thus unclear. However, the prevalence of clinically significant lesions was around 80 per million cases in two studies, one British [1] and the other Belgian [2], of adult European populations. How many of these lesions will show clinical impact is unknown. There are no data for children.

A meta-analysis of 10 retrospective studies including slightly more than 3500 patients reported prevalence of 16.7% for pituitary adenoma and of 0.2% for macroadenoma [3].

1.1. Prevalence of pituitary incidentaloma

Prevalence of pituitary incidentaloma varies depending on the type of examination: 1.4–27% on autopsy and 3.7–37% on imaging [3].

1.1.1. Autopsy series

Prevalence of pituitary incidentaloma on autopsy probably depends on the number and thickness of cross-sections.

In a Japanese series [4], the mean prevalence of pituitary adenoma was 10%, 80% being < 3 mm; macroadenoma was extremely rare. Differential diagnoses comprised Rathke's cleft cyst and craniopharyngioma.

In a recent Iranian study of 485 autopsies, pituitary adenoma was found in 12.6% of subjects, with a mean age of 43 years. Prevalence was unaffected by gender, age or body-mass index (BMI) for both macro- and microadenomas [5]. Other studies, however, reported an age effect, with higher prevalence in elderly subjects [6,7]. The absence of any gender or BMI effect agrees with the rest of the literature, despite the greater frequency of radiologically identified incidentaloma in females [8–11].

1.1.2. Radiological series

The frequency of incidentaloma discovered on imaging is increasing with progress in techniques: CT, 1.5 or 3-Tesla MRI, and PET. The indication for examination also contributes greatly to variation in prevalence. Macroadenoma may cause neurologic symptoms that are not initially seen as implicating adenoma.

1.1.2.1. Overall prevalence. The percentage of serendipitously discovered pituitary masses in a series of 353 consecutive patients seen in a single center over a 14-year period was 12% [12].

1.1.2.2. Prevalence of microincidentaloma. On MRI, focal low-density areas compatible with asymptomatic pituitary microadenoma are found in 10% of healthy subjects [13]. On CT, the percentage varies from 4% to 20% for hyposignal exceeding 3 mm [14–18].

1.1.2.3. Prevalence of macroincidentaloma. On imaging, the prevalence of macroadenoma in healthy populations ranged from 0.11% to 0.3% [16–18] and was 0.2% on CT in an observational study in Ohio [19]. There have been isolated case reports of pituitary incidentaloma discovered on PET scan [20].

1.2. Imaging indications

In a retrospective study of 46 cases diagnosed between 1993 and 2000 [8], patient age ranged between 16 and 77 years, and 63% showed macrotumor. Indications were chronic headache (28%), cranial trauma (15.3%), sinusitis (13%) and stroke (13%). Anterior pituitary deficiency was found in 41.3% of patients, mainly in the form of hypogonadism (30%). Surgery was performed in 37% of cases.

In our own experience, a non-negligible number of microadenomas are discovered on CT following falls, sometimes related to low blood pressure and/or hyponatremia secondary to overlooked hypopituitarism in more elderly patients.

The question of the relationship between headache and pituitary incidentaloma remains open.

1.3. Prevalence according to histologic type

1.3.1. Major prevalences

1.3.1.1. Clinical series. In the clinical series reported by Fainstein Day et al., 30% of surgically managed lesions were gonadotroph adenomas, 40% nonsecreting multi-hormone adenomas, and 30% NF adenomas (i.e., without immunohistochemical reaction to pituitary hormones) [8].

1.3.1.2. Autopsy series. In autopsy series [4,21,22], most adenomas are prolactinomas, although histologically different from prolactinomas in surgical specimens [4]. Various other types (gonadotroph, somatotroph, multi-secreting or nonsecreting adenoma) were also, but less frequently, reported.

1.3.2. Silent corticotroph adenoma

The prevalence of silent corticotroph adenoma in 200 type-2 diabetes patients [23] was 2%. Improved prognosis under treatment for Cushing's syndrome, in terms of hypertension, obesity and carbohydrate intolerance, has so far been found only in clinical case reports. It is to be stressed that corticotroph microadenoma is often difficult to detect on imaging and raises issues of differential diagnosis with respect to nonsecreting incidentaloma.

1.3.3. Other diagnostic pitfalls

1.3.3.1. Thyrotropin-secreting adenoma. The literature highlights the difficulty of distinguishing between thyrotropin-secreting microadenoma and selective pituitary resistance to thyroid hormones associated to a pituitary incidentaloma [24,25].

1.3.3.2. Iatrogenic hyperprolactinemia and incidentaloma. Iatrogenic hyperprolactinemia is another diagnostic pitfall: not so much that induced by psychotropic drugs and anti-emetics, which is well known, as that induced by verapamil (Isoptine®), which, when associated with a pituitary incidentaloma, may give rise to mistaken suspicion of prolactinoma [26].

1.3.3.3. Gonadotroph adenoma. Gonadotroph adenoma can be hard to distinguish from compensated peripheral gonadal insufficiency associated with incidentaloma.

2. Natural history of micro- and macroincidentaloma

To describe the natural history of NF adenoma, we need to look at series of patients managed without surgery by isolated morphologic surveillance. Such studies, however, rarely have long-term follow-up and tend to include small series. Data are sparse, especially for NF microadenoma, although this is the most common form of incidentaloma.

2.1. Nonfunctioning microadenoma

Nonfunctioning microadenoma is the most common form of incidentaloma; depending on the series, 50–90% of incidentalomas are solid tumors, 95% of which are adenomas [17,27]. More than 99% of serendipitously discovered adenomas are microadenomas [3,13,16,18,28]. These percentages agree with autopsy data, with 0.3% microadenomas [29], suggesting that progression from micro- to macroadenoma is very rare. The frequency of microadenoma growth was estimated at 3.3% of patients per year [30]. Increased size was reported in 10 out of 74 microadenoma patients (13%) [27], only 3 of whom had developed macroadenoma by 6–8 years after diagnosis, size increasing in the others by 1–2 mm over periods ranging from 18 months to 10 years; 7 of the 74 actually showed reduction in size. Another study reported 12.5% increase in microadenoma size at 2 years, in 2 out of 16 patients [31]. Molitch reported size increase in 10% of microadenomas and decrease in 6%, at follow-up ranging from 2.5 to 8 years ($n = 160$) [29].

Finally, microadenoma growth is possible but rare (10–13% of cases) and fewer than 5% of lesions grow to more than 1 cm over long-term follow-up, and even so without becoming life-threatening. Increase in size may be found as of 18 months' follow-up but is minimal (1–2 mm); growth to the macroadenoma stage has been reported only with at least 6 years' follow-up.

2.2. Nonfunctioning macroadenoma

Nonfunctioning macroadenoma accounts for about 1% of incidentalomas [3]. Macroadenoma has a greater tendency to grow than microadenoma (12.5% of patients per year vs. 3.3%). Solid lesions show greater progression than cystic lesions (5.7% of patients per year vs. 0.05%) [27,30]. In a series of 115 NF incidentalomas, growth was reported in 20% of cases at 4 years [27]. In a review of 353 macroincidentalomas [29], size increase was found in 24% of cases and decrease in 12%; the rate of increase varied with follow-up: 17% for follow-up < 4 years (38/215) and 34% for follow-up 5–8 years (47/138).

Macroadenoma in contact with the optic chiasm requires morphologic and ophthalmologic surveillance, so as to be able to recommend surgery in case of onset of visual disorder [32,33]. A study of 24 microadenomas, 5 of which were inducing visual disorder at inclusion, found size increase in 50% of cases and

worsening or onset of visual disorder in 67% [33]. Surgical management of NF incidentaloma shows better prognosis than in symptomatic adenoma in terms of 5-year recurrence [34]. The risk of apoplexy is minimal (1%, and 10% at 5 years) but higher in macroadenoma adjacent to the optic chiasm in patients under anticoagulation therapy [17,30,35].

Finally, progression of NF adenoma is associated with the development of anterior pituitary deficiency in 2.4 per 100 patients per year [30]. Certain studies reported improved pituitary function following surgery [36] whereas others did not mention any change or else reported deterioration.

In all, increasing macroadenoma size is reported in 20% of cases at 4 years and in 40% at 8 years. Solid tumors show greater progression than cystic lesions. Surveillance is therefore mandatory in view of the risk of visual impairment and anterior pituitary deficiency.

3. Radiologic differential diagnoses

As seen above, serendipitous discovery of pituitary abnormality on imaging is frequent, with a rate of up to 20% on CT and 38% on MRI [37].

The main diagnostic factors on imaging are based on sella turcica size, exact lesion topology, degree of tumoral uptake, calcification and intralesional fluid level.

This requires repeat MRI centered on the sella turcica, with a rigorous protocol (cf. Raverot et al. in this issue), if the initial examination was for other purposes.

In case of a "solid" mass in the sellar region, the rationales for the various differential diagnoses are the following:

- macroadenomas are centered in the sella turcica, which is enlarged; contrast medium uptake is not intense; there may be small areas of necrotic-hemorrhagic remodeling with variable signal on T1 and T2-weighted sequences; in case of extension into the cavernous sinus, the diameter of the internal carotid artery is respected;
- meningioma of the sellar tubercle does not enlarge the sella turcica. A normal pituitary gland is generally visible under the tumor. Tumor uptake is intense, frequently with a line of enhancement of the dura mater (so-called "comet tail" or "dural tail"), with 75% sensitivity and 94% specificity [38];
- meningioma of the cavernous sinus with extension to but not enlargement of the sella turcica is centered on the cavernous sinus, shows intense enhancement and compresses the internal carotid artery;
- hypophysitis should be systematically considered in women in the peripartum period in case of a mass within and above the sella turcica without enlarging it, showing a regular and harmonious aspect, with intense uptake if injection is possible;
- chordoma may mimic invasive macroadenoma with inferior extension. It is more centered on the clivus than is adenoma, and more precisely on the notochordal remnant, which shows lysis. Extension may be toward the sphenoid sinus then the sella turcica, with lysis of the sellar floor. A normal pituitary gland is usually visible above the tumor. Signal on T2-weighted sequences is often heterogeneous, with variable uptake. There may be intratumoral calcifications;
- depending on the clinical context, consideration should also obviously be given to metastasis to the sellar region (generally, extension to the posterior pituitary lobe, from breast or lung cancer, etc.), or a granulomatosis or lymphoma.

3.1. Cystic mass in the sellar region

In case of cystic mass in the sellar region, the arguments for necrotic adenoma or other differential diagnoses are as follows:

- necrotic macroadenoma is centered on the sella turcica, which is enlarged. A fluid level (best seen on sagittal T2-weighted slice) may be found. The tumor wall shows clear contrast uptake;
- cystic craniopharyngioma may show an aspect similar to that of necrotic adenoma but the sella turcica is often of normal size; intratumoral calcification and absence of fluid level in the cystic part suggest cystic craniopharyngioma;
- strictly medial Rathke's cleft cyst between the anterior and posterior pituitary lobes shows variable signal on T1 and T2-weighted sequences, without uptake, calcification or fluid level;
- arachnoid cyst of the sellar region is easily differentiated from necrotic macroadenoma: although it may enlarge the sella turcica, signal on T1 and T2 is systematically identical to that of the CSF, and the walls show no uptake.

3.2. "Large" pituitary gland

In case of "large" pituitary gland, holosellar adenoma needs to be differentiated from:

- physiological hypertrophy (pregnancy, adolescence);
- pituitary involvement in inflammatory disease, and hypophysitis, usually with a particular clinical context;
- intracranial hypotension syndrome suggested by orthostatic headache associated with other MRI signs of intracranial hypotension, notably hypertrophic pachymeningitis;
- any intrasellar tumor other than adenoma (meningioma, metastasis, etc.), although these are much less frequent. Clinical context (primary cancer, diabetes insipidus [39], etc.) and intense contrast medium uptake generally allow diagnosis.

3.3. Intrasellar "microlesion"

In case of intrasellar "microlesion", microadenoma is suggested by: small mass < 10 mm, often lateralized in the anterior pituitary lobe, slightly deforming the sellar diaphragm, eroding the adjacent floor and pushing back the stalk. Signal may be variable: classically, low signal on T1 and high signal on T2 in GH-secreting microadenoma. Uptake after injection is minimal. Differential diagnosis with respect to Rathke's cleft microcyst and small intrasellar craniopharyngioma is difficult.

4. Essential assessment in pituitary incidentaloma

4.1. Clinical assessment

We recommend primary assessment in endocrinology. Apart from the clinical assessment, this allows the pathology to be explained to the patient, relieving some of the anxiety caused by the discovery of disease when there were no symptoms.

The interview focuses first on history, and particularly familial and personal endocrine history; multiple endocrine pathology is rare, but should be looked for in young patients: type-1 multiple endocrine neoplasia, Carney complex, McCune-Albright syndrome, familial isolated pituitary adenoma, etc.

We then turn to the symptoms that led to serendipitous discovery of probable pituitary adenoma. A possible link with headache (which motivated imaging examination) and pituitary adenoma is to be discussed.

Interview and clinical examination explore possible hypersecretion of prolactin (classically, amenorrhea-galactorrhea syndrome in women, impaired libido, gynecomastia in men), GH (signs of acromegaly) or ACTH (clinical or infraclinical Cushing's syndrome).

In case of lesions suggesting macroadenoma, signs of hypopituitarism and/or tumoral syndrome (headache, chiasm syndrome) should be looked for.

In large lesions close to the optic chiasm, chiasm syndrome should be looked for, firstly by clinical finger analysis of the visual field to screen for bitemporal hemianopsia; results are to be confirmed by visual field examination by an orthopist.

The 2011 Endocrine Society guidelines [37] are in agreement with the above.

4.2. Essential biological assessment

The Endocrine Society guidelines [37] recommend systematic full clinical and biological assessment in all cases of pituitary incidentaloma. The biological assessment comprises: exploration for systematic prolactin and GH hypersecretion and, in case of Cushing's syndrome, exploration for cortisol and ACTH hypersecretion; and exploration for hypopituitarism, with assays of all anterior pituitary hormones and the corresponding peripheral hormones.

The present French consensus document focuses on serendipitously discovered adenoma, with a distinction drawn between microadenoma (or microincidentaloma) and macroadenoma (or macroincidentaloma), unlike in the 2011 Endocrine Society guidelines [37]. This distinction appeared appropriate, and we shall present the rationale, always bearing in mind an important aspect: that of cost.

4.2.1. Serendipitously discovered microadenoma

4.2.1.1. Is it recommended to explore for prolactin, GH or ACTH hypersecretion?. The factors to be considered here are the following: increasing incidence of discovery of such lesions, due to increasing use of imaging; respective frequencies of the various histologic types of microincidentaloma found in surgical and autopsy series (NF/gonadotroph adenoma is much more frequent than prolactinoma, which in turn is more frequent than somatotroph adenoma, which in turn is more frequent than corticotroph adenoma; cf. Epidemiology section above); hormone assay costs; and the lack of evidence in the literature (small heterogeneous series).

4.2.1.1.1. Should prolactin assay be systematic?. The literature, although still insufficient, now provides enough justification for prescribing prolactin assay. The series are small and heterogeneous but, epidemiologically, prolactin-secreting microincidentalomas are fairly frequently reported: 5 out of 42 microincidentalomas, all in female subjects, in Feldkamp et al.'s series [40], and 7 out of 46 incidentalomas (not distinguishing micro- and macroincidentaloma), all in male subjects, in Fainstein Day et al.'s series [8]. Some older series, on the other hand, find none [41,42]. Finally, in a large autopsy series, 132 out of 334 adenomas (39.5%, all microadenomas of 0.1 to 6 mm diameter, median 1.2 mm) were prolactin-positive on immunolabeling [43].

4.2.1.1.2. Particular situations in prolactin assay. Moderately elevated prolactinemia suggests macroprolactinemia (aggregates of prolactin molecules without any clinical consequence). By definition, this prolactin assay artifact is not associated with any symptoms of hyperprolactinemia (cf. Raverot et al.).

Guideline:

- systematic prolactin assay is recommended in case of microincidentaloma suggesting microadenoma.

4.2.1.1.3. Should IGF-1 assay be systematic?. According to the currently available epidemiological data, somatotroph adenoma is rare and mainly comprises macroadenoma. One of the main reasons for this is late diagnosis of GH hypersecretion, as clinical signs develop very slowly and are long overlooked. The considerations to be taken into account in recommending systematic IGF-1 assay or not are the following:

- do somatotroph microadenomas immediately secrete enough GH to elevate IGF-1 levels; what is the threshold tumor volume beyond which IGF-1 is elevated in case of GH-secreting adenoma? What is the natural history of GH-secreting adenoma? Unfortunately, there are at present no clear answers to these questions;
- are GH-secreting microincidentalomas frequent enough for systematic IGF-1 assay to be recommended? Here again, the literature is limited, as series were small. Silent somatotroph adenoma is rare. A series of 3048 autopsies reported 334 adenomas, including 1.8% positive for GH on immunolabeling [43];
- the cost of systematic assay is to be borne in mind;
- the Endocrine Society guidelines [37] suggest systematic IGF-1 assay for all pituitary incidentalomas. The rationale is based on the above epidemiological considerations and on

the fact that treatment of somatotroph adenoma is surgical and GH-secreting microadenoma could be cured by surgery.

Guideline:

- systematic IGF-1 assay is recommended in hormonal assessment of microincidentaloma.

4.2.1.1.4. Should there be systematic exploration for cortisol hypersecretion?. Here again, the argument is based on epidemiology. Secreting corticotroph adenoma (implicated in clinical Cushing's syndrome) is rare, and mainly in the form of microadenoma. In a series of 3048 autopsies, 13.8% of the 334 pituitary adenomas expressed ACTH [43]. At present, there are no reported cases of infraclinical Cushing's syndrome associated with pituitary microadenoma.

Guideline:

- it would not seem useful to explore for cortisol hypersecretion in pituitary microincidentaloma (asymptomatic by definition).

Certain teams prescribe ACTH assay [44]. But ACTH may be elevated without biological evidence of cortisol hypersecretion, hindering indications.

Guideline:

- exploration for cortisol hypersecretion and/or ACTH assay are not recommended systematically but only in case of clinical signs of Cushing's syndrome. (This chapter does not deal with biological diagnosis of Cushing's syndrome.).

The above is in agreement with Endocrine Society guidelines [37].

4.2.1.1.5. Is systematic dynamic testing recommended to explore for hormonal hypersecretion?. The interest of dynamic testing to explore for hormonal hypersecretion (other than hypercorticism) is highly controversial (cf. Raverot et al.).

Guideline:

- systematic dynamic testing is not recommended.

4.2.1.2. Should anterior pituitary insufficiency be explored for in case of pituitary microincidentaloma?. There is only one publication on this subject [45]. Fifty percent of the 38 patients with NF pituitary microadenoma showed anterior pituitary insufficiency, defined by at least one deficit. The most frequent deficit was for GH, shown on dynamic testing (GHRH-Arginine) with normal IGF-1 levels. The second was thyrotropin deficit. This study is alone in going against the classic concept according to which only macroadenoma can induce anterior pituitary insufficiency.

There have been no prospective studies comparing anterior pituitary insufficiency according to microincidentaloma size.

The Endocrine Society guidelines for pituitary incidentaloma [37] took account of the above-mentioned publication, recommending exploration for anterior pituitary insufficiency in case of large microincidentaloma (e.g., 6–9 mm).

Guideline: systematic exploration for anterior pituitary insufficiency in case of pituitary microincidentaloma is not recommended. Exploration for anterior pituitary insufficiency, and for somatotropic insufficiency in particular, may be considered in 6–9 mm pituitary microincidentaloma if GH replacement therapy is likely to be prescribed. Diagnosis requires dynamic testing.

4.2.2. Macroincidentaloma

Initial assessment of pituitary macroincidentaloma should be performed as for NF adenoma with clinical consequences. This will not be dealt with here, and is discussed in Raverot et al.

4.3. Assessment of visual impairment

Guideline:

- visual assessment is not useful in suspected microadenoma;
- nor is it recommended if the lesion is remote from the optic chiasm;
- it is, however, recommended if the lesion is close to the optic chiasm or is seen to be compressing it on MRI.

Examination is performed by an ophthalmologist, following the procedure recommended in the present consensus document (cf. Abouaf et al.). The diagnosis of chiasmal syndrome is critical to treatment strategy, and especially for indications for surgery (see below).

The Endocrine Society guidelines [37] are in agreement with this.

4.4. Role of biopsy in case of difficult radiologic interpretation

If radiologic diagnosis shows likely pituitary adenoma, there is no reason to perform biopsy.

Indications for biopsy in pituitary lesions are not well documented in the literature.

In lesions that are difficult to characterize radiologically and/or impossible to remove, biopsy may be considered, to guide treatment.

4.5. Medical economic aspect

Health economics is certainly to be taken into account in managing pituitary incidentaloma, given its frequency. There are, however, no updated publications comparing options from the medical economic point of view. A single paper, from 1997, studied cost/benefit and quality of life impact for 4 types of microincidentaloma management:

- clinical surveillance;
- isolated prolactin assay, repeated only in case of elevation;
- various hormone assays, including prolactinemia, IGF-1, cortisolemia after minute suppression with 1 mg dexamethasone;
- MRI surveillance at 6 and 12 months [46].

It was concluded that the second (isolated prolactin assay) showed the best cost/benefit ratio.

5. What type of management?

5.1. Surveillance?

If surgery is not initially indicated, morphologic, hormonal and ophthalmologic surveillance should be adapted to clinical presentation: initial adenoma size, proximity to the optic chiasm, hormonal deficits, and patient age. The rationale of surveillance concerns the risk of progression, especially in macroadenoma, with possible onset of visual or hormonal effects.

As seen above, size increase, even in macroadenoma, is not systematic. On average, 89% of microadenomas and 75% of macroadenomas remain stable over 2–8 years' follow-up. Other than in situations in which surgery is the first-line option in patients free of comorbidity (proximity to or compression of the chiasm), surveillance is the logical attitude.

5.1.1. Surveillance of NF microincidentaloma

It is to be borne in mind that NF microincidentaloma is very frequent (found in 10–15% of MRIs). The present guidelines seek to minimize the extra cost of inappropriate close surveillance and to reduce the anxiety of the patient (and of the physician!).

Guidelines:

- in NF microadenoma of ≤ 5 mm diameter, neither radiologic nor hormonal surveillance are recommended: it is more important to reassure the patient;
- in NF microadenoma of > 5 mm diameter, simple morphologic surveillance in 6-month MRI is recommended, without visual or hormonal exploration. If there is no progression, MRI may be repeated at 2 years, without visual or hormonal exploration, and, if there is no progression, morphologic surveillance can then be stopped;
- in case of progression (bearing in mind that microadenoma rarely evolves into macroadenoma), MRI surveillance may be closer (e.g., annual), to guide treatment or continued surveillance

5.1.2. NF macroincidentaloma

Macroadenoma increases in size more often than microadenoma, which, given its initial size, may cause visual disorder. This requires closer surveillance than for microincidentaloma.

The American consensus [37] recommends MRI at 6 months then annually for 3 years, then less frequently (whether the lesion is close to the optic chiasm or not).

Guidelines for NF macroincidentaloma remote from the optic chiasm (suggested criterion: 5 mm):

- MRI at 1 year, if no clinical progression, with hormone exploration for anterior pituitary insufficiency. Visual exploration (visual field and acuity) in case of adenoma in contact with the chiasm on surveillance;
- for macroadenoma remote from the chiasm, with no tumoral progression at 1 year, MRI surveillance can be 2-yearly, if no clinical progression. Hormone exploration for anterior pituitary insufficiency can be annual. Visual exploration (visual field and acuity) in case of adenoma in contact with the chiasm on surveillance. Visual assessment is described in Abouaf et al.

Guidelines for NF macroincidentaloma close to or in contact with the optic chiasm:

- if surgery is not indicated, MRI should be performed at 6 months, with hormone exploration for anterior pituitary insufficiency and visual exploration (visual field and acuity). MRI surveillance should thereafter be annual, with hormone exploration. Visual exploration can be 6-monthly;

- in case of visual impact, tumor progression or anterior pituitary insufficiency, surgery may be proposed (seeing following subsection). If surveillance is continued (comorbidity, etc.), it should continue as above.

5.2. What indication(s) for surgery?

Incidentaloma should be managed by a reference multidisciplinary team experienced in pituitary surgery, as complication rates correlate with experience [47].

The technique (preferably endonasal endoscopic) and approach (transsphenoid except in case of posterior and lateral intracranial extension toward the Sylvian fissure) do not vary whether discovery is serendipitous or not, but only according to tumoral anatomy.

In absence of symptoms, informed discussion with the patient is especially important.

In NF incidentaloma, indications for surgery depend:

- on tumor anatomy (large volume; cystic aspect or not; cavernous sinus invasion);
- on clinical criteria (age, physiological status, comorbidity, etc.);
- on endocrine or ophthalmologic deficit.

5.2.1. NF microincidentaloma

In asymptomatic enclosed intrasellar forms not in contact with the optic chiasm, surveillance as described above is a justifiable attitude. Tumor regression, reported in 10–29% of cases, argues for such non-intervention [33,48]. Only progression indicates surgery; no threshold size increase can be specified, as age, comorbidity and proximity to the chiasm are also to be taken into account: the decision is to be made on a case-by-case basis, in discussion with the patient [37].

5.2.2. NF macroincidentaloma

5.2.2.1. NF macroincidentaloma with normal assessment results. In NF macroincidentaloma with normal assessment results, decision-making is based on the natural history of pituitary adenoma, the postoperative reversibility of ophthalmic and/or endocrine symptoms, and the clinical context.

Given an aspect of adenoma on imaging, surveillance on the above schedule should be considered if there is a safety margin with respect to the chiasm (e.g., 2–3 mm), especially in elderly patients and/or in case of comorbidity. Invasion of cavernous space is not a reason for active primary treatment, as surgery will not cure the patient. If there is no contact with the visual pathway, there is no reason for ophthalmologic follow-up. Tumor progression (no specified threshold) indicates surgery.

In four particular cases, surgery is indicated as primary treatment:

- desire for pregnancy in the short-term, given the risk of growth of incidentalomas/adenomas during pregnancy (see guidelines in Castinetti et al., in the present consensus document);
- differential diagnostic doubt with respect to malignancy (although malignant lesions are rarely asymptomatic);
- non-compliant patient liable to escape follow-up;
- and associated NF pituitary macroadenoma, male gender, proximity to chiasm and anticoagulation therapy, as this entails elevated risk of apoplexy, which can have serious consequences [35]: first-line surgery can be discussed with the patient, depending on the risk associated with interruption of anticoagulation therapy.

If the distance from the chiasm is short or there is contact, first-line surgery should be discussed with the patient, based on:

- risk of progression and symptom onset reported in follow-up studies (20–50% rates of increasing volume over 5 years) [17,27,48];
- risk of apoplexy (depending on the report, 10% at 5 years [17] or 1.6% to 12.8% [35] with risk of ophthalmologic disorder and definitive endocrine deficiency [35]);
- better ophthalmologic and endocrine results reported in asymptomatic patients [34,49].

The context may, however, make surveillance or abstention preferable (elderly patient with comorbidities, or refusal of surgery).

5.2.2.2. Symptomatic NF macroincidentaloma. The Endocrine Society guidelines favor surgical management [37].

We also recommend discussing surgery in case of visual disorder and/or anterior pituitary insufficiency.

The context may, however, make surveillance or abstention preferable (elderly patient with comorbidities, or refusal of surgery). Medical treatment (dopaminergic agonists, somatostatin analogs) may be discussed (see guidelines in Cortet-Rudelli et al., in the present consensus document).

6. Decision-tree for the management of pituitary incidentaloma

The decision-tree below (Fig. 1) encapsulates the recommendations for the management of pituitary incidentaloma.

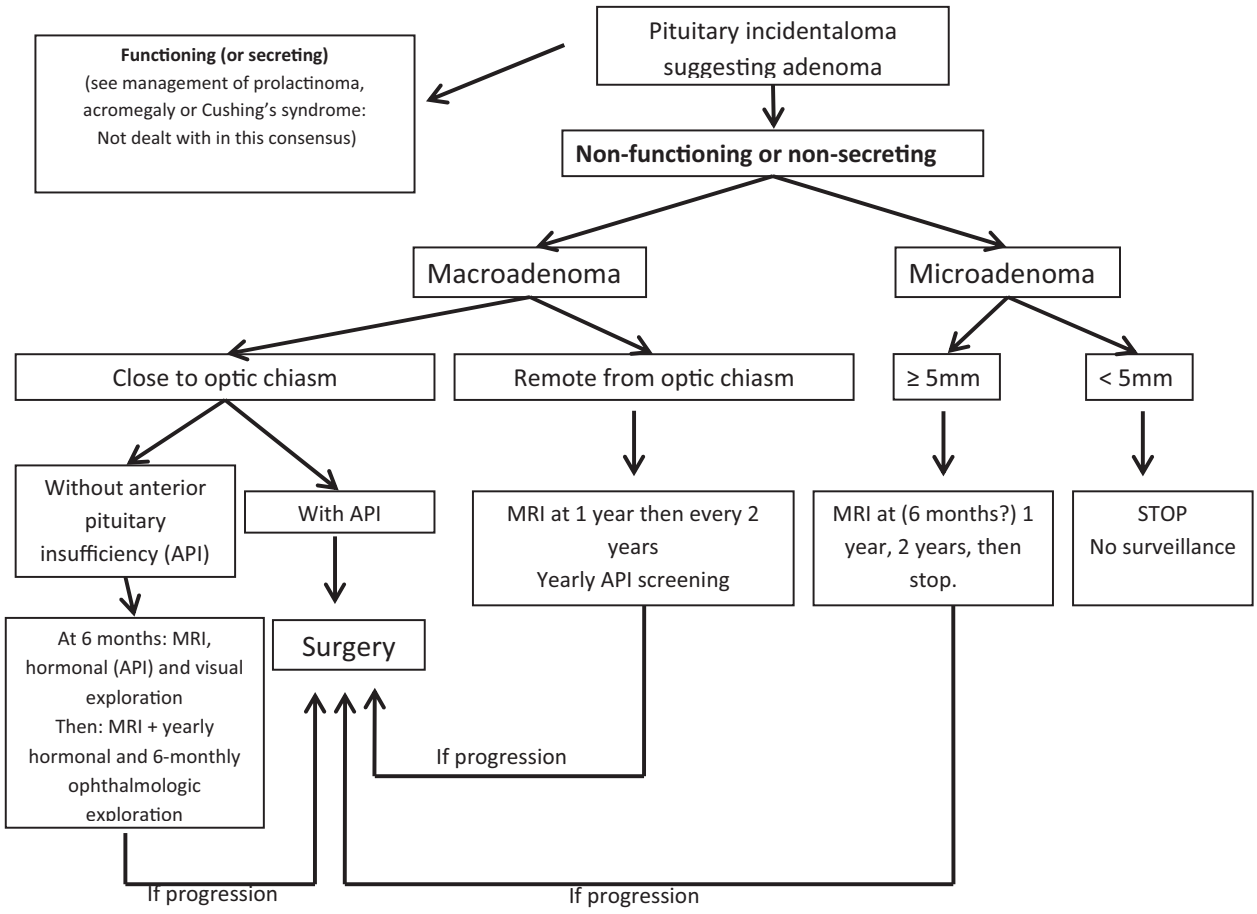

Fig. 1. Decision-tree for the management of pituitary incidentaloma.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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