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Consensus

Management of clinically non-functioning pituitary adenoma☆

Prise en charge des adénomes hypophysaires cliniquement non fonctionnels

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Abstract

Clinically NFPA is currently the preferred term for designing all the pituitary adenomas which are not hormonally active (in other words, not associated with clinical syndromes such as amenorrhea-galactorrhea in the context of prolactinomas, acromegaly, Cushing's disease or hyperthyroidism secondary to TSH-secreting adenomas). They account for 15–30% of pituitary adenomas. Diagnosis is usually made either in the context of mass effect due to a macroadenoma or, increasingly, fortuitously during imaging performed for some unrelated purpose; the latter case is known as pituitary incidentaloma. Surgery is indisputably indicated in case of tumoral syndrome, but other aspects of NFPA (hormonal work-up, follow-up, and especially postoperative follow-up, management of remnant or recurrence, the special case of incidentaloma, or apoplexy) remain controversial. The French Endocrinology Society (SFE) therefore set up an expert working group of endocrinologists, neurosurgeons, ophthalmologists, neuroradiologists, pathologists and biologists to draw up guidelines, at the 2012 SFE Congress in Toulouse, France. The present article presents the guidelines suggested by this group of French-speaking experts.

Keywords: Non-functioning pituitary adenoma; Gonadotroph adenoma; Silent pituitary adenoma; Pituitary apoplexy; Pituitary incidentaloma; Non-secreting pituitary adenoma; Pituitary surgery; Radiation therapy

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☆ Consensus of the French Endocrine Society: non-functioning pituitary adenoma.

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Résumé

Les adénomes hypophysaires non fonctionnels (AHNF) qui se définissent par défaut (ce ne sont ni des prolactinomes, ni des adénomes somatotropes responsables d'acromégalie, ni des adénomes corticotropes responsables de maladie de Cushing) représentent 15 à 30 % des adénomes hypophysaires. Leur diagnostic est le plus souvent fait à l'occasion, soit d'un syndrome tumoral, lié à la présence d'un macroadénome, soit (et c'est de plus en plus fréquent) de manière fortuite à l'occasion d'une imagerie faite pour une toute autre raison (ce sont les incidentalomes hypophysaires). Si l'indication chirurgicale ne fait aucun doute en cas de syndrome tumoral, d'autres aspects des AHNF (l'exploration hormonale, le suivi, en particulier postopératoire, la conduite à tenir en cas de reliquat ou en cas de récidive, le cas particulier des incidentalomes, ou de l'apoplexie) font l'objet de discussions, qui ont amené la Société française d'endocrinologie (SFE) à demander à un groupe d'experts (endocrinologues, neurochirurgiens, ophtalmologistes, neuroradiologues, pathologistes et biologistes) de formuler des recommandations à l'occasion du Congrès de la Société française d'endocrinologie qui s'est tenu à Toulouse en 2012. Cet article résume les recommandations proposées par ce groupe d'experts francophones.

Mots clés : Adénomes hypophysaires non fonctionnels ; Adénomes gonadotropes ; Adénomes hypophysaires silencieux ; Apoplexie hypophysaire ; Incidentalomes hypophysaires ; Adénomes hypophysaires non sécrétants ; Chirurgie hypophysaire ; Radiothérapie

Clinically non-functioning pituitary adenomas (NFPA) is currently the preferred term for designing all the pituitary adenomas which are not hormonally active (in other words, not associated with clinical syndromes such as amenorrhea-galactorrhea, acromegalic features, hypercorticism or hyperthyroïdism). Since 1979–1980, with progress in immunocytochemistry [1–3], it has been known that most "clinically non-functioning" adenomas (chromophobe on classic histology) actually secrete gonadotropins or are gonadotroph pituitary adenomas. In 10% of cases, immunolabeling is negative ("null-cell adenoma"). Exceptionally, it may be positive for GH, PRL, TSH or ACTH despite no secretion being found in vivo; such cases are known as silent somatotroph, lactotroph, thyrotroph or corticotroph adenomas.

Prevalence of pituitary adenoma is 80–100 cases per 100,000 of the population; NFPA accounts for 15–30% of these [4–6]. Annual incidence is 1 new case per 100,000 of the population [4].

At the present time, NFPA are diagnosed either in the context of mass effect related to the growth of a macroadenoma or, increasingly, fortuitously during imaging for some unrelated purpose; the latter case is known as pituitary incidentaloma [7,8].

Surgery is indisputably indicated in case of tumoral syndrome, but other aspects of NFPA (hormonal exploration, follow-up, and especially postoperative follow-up, management of postoperative remnant or recurrence, the special case of incidentaloma, or apoplexy) remain controversial. The French Endocrinology Society (SFE) therefore set up an expert working group of endocrinologists, neurosurgeons, ophthalmologists, neuroradiologists, pathologists and biologists to draw up guidelines, at the 2012 SFE Congress in Toulouse, France.

In the absence of prospective, randomized controlled studies, the group could put forward only expert opinions, at best founded on retrospective studies.

1. Biochemical, neuroradiologic and clinical assessment of non-functioning pituitary adenomas

Pituitary macro-adenomas, whether discovered in the context of a mass effect or fortuitously, require various explorations before surgery can be indicated.

The aim is to assess pituitary hormone secretion, looking either for hypersecretion (confirming non-functioning status) or deficiency, which may require preoperative hormone replacement therapy. The aim is also to provide the surgeon with good pituitary imaging. Finally, inasmuch as indications for surgery are closely dependent on optic pathway compression, optic pathway assessment is also indispensable, preoperatively and during follow-up.

The present guidelines are founded on a review of the literature, the details of which are given in the article by Raverot [9] in the present Consensus document.

1.1. Diagnostic hormonal work-up to screen for pathological secretion

Half of the male and one-quarter of premenopausal female patients with NFPA display increased levels of gonadotropins. Response of gonadotropins and free sub-units to TRH and GnRH stimulation tests are neither sensitive nor specific for the diagnosis of the gonadotroph nature of the NFPA [9].

1.1.1. Static exploration

Preoperatively, systematic gonadotropin (LH, FSH) measurement is recommended for allow preoperative diagnosis of gonadotroph adenoma (in case of increased levels of FSH and/or LH), but it does not affect the treatment or follow-up of NFPA.

Sub-unit α measurement may be contributive, but should not be systematic, especially as it is not covered by the French National Health Insurance System (unlisted analysis).

Prolactin (PRL) measurement is systematic in NFPA. In large pituitary adenoma, PRL measurement should be performed with 1/100 serum dilution, to avoid hook effect which may mask very high levels of PRL levels suggestive of prolactinomas.

Chromogranin A measurement is not recommended for diagnosis or follow-up.

1.1.2. Dynamic testing

GnRH or TRH stimulation tests are not recommended for diagnosis or follow-up of NFPA, being insufficiently

contributive and incurring a rare but serious risk of pituitary apoplexy.

1.1.3. Screening for silent pituitary adenoma

"Silent" adenoma would seem to be of poorer prognosis (cf. article by Cortet-Rudelli in the present Consensus document [10]) with more frequent recurrence. Silent pituitary adenoma is defined by the absence of suggestive preoperative clinical signs of secretion associated with positive immunolabeling of the operated tumor for one or more hormones.

Only corticotroph silent adenoma can be detected preoperatively, with increase in ACTH levels and normal 8.00 a.m. cortisol, or with absence of corticotroph deficit while all other pituitary hormones are deficient [9]. An overnight dexamethasone-suppression test (1 mg dexamethasone at midnight and measurement of cortisol and ACTH levels eight hours later) may be contributive (and is systematic in some centers), as may be free urinary cortisol measurement.

In silent somatotroph adenoma, IGF-1 levels are by definition normal; otherwise, acromegaly should be diagnosed, even in absence of clear clinical signs (cf. Acromegaly Consensus [11]).

In silent lactotroph adenoma, prolactin assay is normal and diagnosis is founded on positive tumor immunolabeling for PRL.

1.2. Screening for hypopituitarism

At time of diagnosis of non-functioning pituitary macroadenomas, 60 to 85% of patients present at least one pituitary deficiency, gonadotroph deficiency being the most prevalent (>80% of cases), followed by the somatotroph deficiency; thyrotroph and corticotroph deficiencies are found in 20–50% of cases [9].

1.2.1. Hormonal tests

Screening for corticotroph deficiency requires, for many teams, a preoperative dynamic test: insulin tolerance test, ACTH stimulation test, CRH test or metyrapone test. Other teams only perform measurement of morning cortisol: a level of >190 ng/ml (500 nmol/l) confirming corticotroph integrity, making dynamic testing superfluous.

Screening for thyrotroph deficiency screening is based on free T4 measurement associated to third generation TSH assay.

Screening for gonadotroph deficiency in female subjects is based on clinical assessment, if necessary associated to plasma gonadotropin (LH and FSH) measurement. In male subjects, plasma gonadotropin (LH and FSH) levels and total testosterone measurement are required.

1.2.2. Assessment at diagnosis

Screening for pituitary gonadotroph, corticotroph and thyrotroph deficiency is recommended at diagnosis of any pituitary adenoma, but only of macroadenoma. Preoperative detection of deficiency enables treatment to improve clinical status ahead of surgery or, if surgery has not been decided on, to monitor hormonal status during follow-up, notably in case of corticotroph deficiency, and guides therapeutic decision-making (cf. incidentaloma). Screening for somatotroph deficiency is not recommended at diagnosis.

1.2.3. Monitoring of pituitary function after surgery

Corticotroph function should be assessed either in the immediate postoperative period or at 4–6 weeks with systematic hydrocortisone replacement in the interval. In case of deficiency, further exploration should be performed at least by 3 months postoperatively, to screen for late recovery.

Global pituitary function should be assessed 1–3 months post-surgery. If there is no postoperative deficiency, further exploration is unnecessary unless there is progression in a tumor remnant or occurrence of a recurrence. In case of postoperative deficiency, 6–12 monthly monitoring is required to tailor replacement therapy.

If there is no postoperative deficiency, 6–12 monthly monitoring is required if adjuvant radiation therapy is to be implemented.

Preoperative thyrotroph deficiency should be reassessed postoperatively after at least 1 month's interruption of thyroxine therapy.

1.3. Pituitary imaging

1.3.1. Neuroradiological assessment of suspected NFPA

Neuroradiological assessment of suspected NFPA is founded on MRI, the reference examination for the sellar region.

1.3.2. MRI protocol

The MRI protocol should include:

- thin ($\leq$3 mm) slices, high matrix, sagittal + coronal T1-weighted sequences with and without gadolinium injection;
- coronal 3D volume assessment with reconstruction;
- T2-weighted coronal slices;
- volume acquisition is recommended; otherwise, very thin slices are needed, with a reference plane (e.g., subcallosal).

1.3.3. Typical MRI aspects of NFPA

Typical MRI aspects of NFPA are as follows:

- in macroadenoma, a mass centered on an enlarged sella turcica, with T1/T2 signal varying according to necrotic and/or hemorrhagic areas, possibly with fluid level;
- enhancement of the lesion is usually of low intensity.

The necrotic or hemorrhagic nature and extension of the lesion should be determined:

- superiorly, toward the optic pathways;
- laterally, in the cavernous sinuses, taking account of percentage tumoral inclusion of the internal carotid artery (arterial diameter generally conserved) and visibility of medial cavernous sinus veins;
- inferiorly, in the sphenoidal sinus, with sellar floor lysis and, posteriorly, lysis of the clivus.

The pituitary stalk, posterior lobe and healthy residual pituitary parenchyma should be located.

1.4. Ophthalmologic assessment of NFPA

Neuro-ophthalmologic exploration is one of the major determinants of surgical indications. The present guidelines are based on a literature review detailed in the article by Abouaf [12] in the present Consensus document.

1.4.1. Ophthalmologic assessment

Ophthalmologic assessment should comprise:

- sensory evaluation: at least one measurement of visual acuity (VA) and a visual field examination (VF), preferably central static + peripheral kinetic. Anterior segment and fundus examinations are also essential for interpreting the VA and VF data; OCT is contributive but not essential for determining visual prognosis;
- oculomotor evaluation: diplopia should be ruled out on interview, checking the patient's 9 gaze directions. This may be completed by orthoptic examination and the Lancaster test.

1.4.2. When to perform ophthalmologic exploration?

At diagnosis, within 3 months of surgery, and ahead of any radiation therapy (RT) in case of adenoma abutting or compressing the optic chiasm.

Subsequent follow-up depends on visual involvement and progression, and on scheduled RT.

2. Surgical treatment of non-functioning pituitary adenomas

No effective medical treatment being available, as in the case of prolactinoma or somatotroph adenoma, first-line treatment of NFPA is surgical, usually with a trans-sphenoidal approach.

The present guidelines for surgery are based on a literature review detailed in the article by Castinetti [13] in the present Consensus document.

2.1. Indications for surgery

2.1.1. In symptomatic macroadenoma

2.1.1.1. Visual disorders. Visual disorders are an indication for surgery, urgency depending on the degree of visual impairment. Recovery correlates with duration and severity of VF defect; improvement is reported in about 80–90% of cases, up to 1 year post-surgery [13].

2.1.1.2. Hypopituitarism. Hypopituitarism should be taken into account for deciding to treat surgically, as postoperative recovery is uncertain (around 30% of cases), with a 5–10% risk of aggravating or inducing hypopituitarism. The risk of onset of diabetes insipidus is less than 5%.

2.1.1.3. Mass effect. Pituitary adenoma cannot be incriminated in headache until all other causes have been ruled out (possibly after neurologic consultation). Disabling headache implicating the adenoma may thus be an indication for non-emergency surgery, but the patient should be warned that causality is unproven and relief cannot be guaranteed.

In large adenoma without visual disorder, the decision is made on an individual basis and is founded on the kinetics of progression on two successive MRI scans.

2.1.2. Surgical indications for particular situations

Indications in older subjects (aged 65 to 75–80 years). They are identical to those in younger subjects if comorbidity and anesthesia risk are well assessed (ASA score [American Society of Anesthesiology: http://www.asahq.org]). The principal indication is visual involvement. Surgery, if decided on, should preferably be trans-sphenoidal, in order to limit the risk of complications. In "physiologically elderly" subjects, surgical risk is elevated and indications should be weighed on a case-by-case basis, with the sole objective of optic chiasm decompression.

Indications in patients taking anti-platelets or anticoagulants. Treatment with anti-vitamin K increases the risk of spontaneous cerebral hemorrhage 7–10-fold and interruption, with use of heparin in the interval, is recommended 5 days ahead of surgery, to achieve a normal INR (international normalized ratio); anti-vitamin K will be reinitiated within 7–14 days. Anti-platelets increase the risk of postoperative hematoma, but preoperative interruption is associated with increased morbidity and mortality, especially in drug-eluting stent bearers, and requires the agreement of a cardiologist, 5 days before surgery for aspirin and ideally 10 days for clopidogrel, with resumption theoretically 7–10 days post-surgery.

2.1.3. Asymptomatic micro- or macro-adenomas

Asymptomatic micro- or macro-adenomas are generally discovered fortuitously on MRI performed for some other reason. Management and surgical indications are dealt with in section 5, The particular case of non-functioning pituitary incidentaloma.

2.1.4. NFPA developing during pregnancy

In case of NFPA developing during pregnancy and inducing visual disorder, surgery is mandatory. If there is no chiasmal compression during pregnancy, delivery can be vaginal. Breast-feeding is in no way contraindicated.

2.2. Surgical technique

2.2.1. Endoscopy versus microsurgery?

More than the technique as such, it is the neurosurgeon experience that is essential in the management of pituitary adenomas, and the choice is at the discretion of the surgeon. Endoscopy is probably preferable to microscopy, providing better control of lateral and superior extension for an identical rate of complications but this has not been clearly demonstrated [13].

2.2.2. Technical specificities

The choice between the various approaches (2-step surgery, trans-sphenoidal extended approach, trans-cranial approach) is

at the surgeon's discretion, according to experience and adenoma extension. Approaches are limited to specific types of adenoma, according to extension. More specific techniques (neuronavigation, intraoperative MRI) may be used if the surgeon judges necessary and they are available.

3. Pathologic diagnosis of non-functioning pituitary adenomas

The pathology report should include certain information indispensable to diagnosis and subsequent management, as detailed in the appendix to the article by Castinetti in the present Consensus document [13]. Teamwork between endocrinologist, neurosurgeon and pathologist is required: final pathologic diagnosis of NFPA should also take into account imaging data and intraoperative findings, to assess tumor size and invasiveness toward the cavernous and/or sphenoidal sinuses.

Immunohistochemistry allows to determine the nature of the adenoma: gonadotroph (βFSH, βLH, αSU, chromogranin A antibodies) or silent somatotroph and/or lactotroph (GH, PRL antibodies) or corticotroph adenoma (ACTH antibodies, cytokeratin). The pathology reports also need to establish proliferation status by systematically testing three types of cell-cycle markers: Ki67, mitosis index and p53 [13].

4. Postoperative management of pituitary non-functioning pituitary adenomas

Despite progress in neurosurgery, the size and frequent invasiveness of NFPA often result in partial resection, and the remnant is susceptible to regrow (at 10 years, half have regrown) [10]. Moreover, even when resection is total, recurrence is possible, even if are (30% at 10 years) [10]. In either case, complementary treatment (surgical revision, radiation therapy, medical treatment) may be indicated. The following guidelines are founded on the literature data detailed in the article by Cortet-Rudelli in the present Consensus document [10].

4.1. Postoperative follow-up of NFPA

4.1.1. Follow-up imaging

Postoperative radiologic monitoring is essential in NFPA due to the frequent lack of any clinical symptoms despite progression. It is best performed on MRI, with pituitary CT only in case of contraindications. Reproducibility is indispensable to good follow-up, and is ideally achieved by volume acquisition with 3D reconstruction. If the latter is unavailable, scans should be taken under constant technical conditions with an identical reference plane: e.g., coronal slices perpendicular to the subcallosal plane. It is important to provide the neuroradiologist with the preoperative MRI scan, surgical report and reference postoperative MRI, for purposes of interpretation. The imaging protocol comprises thin (2–3 mm) slices: T1-weighted sagittal, T1-weighted coronal T1 before and after gadolinium injection, and T2-weighted coronal or T1-weighted axial.

Regarding the frequency of postoperative MRI, immediate examination is not systematic but may be prescribed for suspected postoperative complications or in case of early revision surgery within the first days. Otherwise, the first MRI is at 3 or 6 months; a 6-month interval minimizes difficulties of interpretation due to postoperative remodeling. A second MRI is systematically performed one year post-surgery. These two MRIs serve as references for subsequent follow-up.

Precise interpretation of the reference postoperative MRI is primordial, to detect residue and thus risk of progression. In the absence of adenomatous residue, MRI is repeated annually for 5 years, then at 7, 10 and 15 years. In the absence of clinical signs, identifiable residue or suspect images, systematic radiological follow-up may then be terminated. In case of adenomatous remnant or suspect image, MRI is repeated annually for 5 years and then every 2 or 3 years in the absence of progression, and the schedule is redefined on a case-by-case basis according to tumor size, remnant distance from the optic pathways or any doubt as to remnant progression. Longer intervals incur a risk of loss to follow-up, requiring special vigilance, recurrence usually occurring 1–5 years after surgery but sometimes later, at more than 10 years [10].

At each control, it is essential to check the new image against the postoperative references: gradual increase in residue size might be overlooked if the new MRI is compared only with the preceding one and not with the postoperative reference, as adenoma growth is often slow and hard to discern from one year to the next.

4.1.2. Ophthalmologic follow-up

In case of preoperative ophthalmologic abnormality, a check-up is made at 3 months post-surgery, comprising VA, VF, fundus and oculomotor examination, and repeated every 6 months until maximal improvement is achieved, especially if initial disorder was severe or contraindicated driving; such contraindications should be reviewed regularly during follow-up. Surveillance intervals may then be lengthened.

In the absence of visual impairment at the first postoperative visit, follow-up can stop if there is no suprasellar remnant threatening the optic pathways. In case of radiation therapy, prolonged annual follow-up is mandatory, especially after hypofractionated or single-dose radiation therapy, to screen for radiation-induced complications, which may occur several years post-treatment.

4.1.3. Hormonal follow-up

Biochemical hormonal assessment at 3 months post-surgery focuses on recovery of preoperative pituitary deficiencies and on the definitive nature of deficiencies found postoperatively. Exploration is then repeated to adapt, if necessary, replacement therapies in case of functional alarm signs or increased size of any residue. The frequency of pituitary deficiency following RT of whatever type requires twice-yearly reassessment as above.

Deficits, obviously, require replacement. GH treatment is at the physician's discretion, in the light of the fact that the literature now supports the absence of any stimulation of remnant or induction of recurrence.

4.2. When is simple surveillance indicated?

4.2.1. In the absence of identifiable adenomatous remnant or in case of suspect image

Prolonged regular surveillance is recommended, the risk of complications associated with reoperation being lower than that of recurrence and/or recurrence-related complications.

4.2.2. In case of remnant

Two options are available: simple surveillance or adjuvant therapy. Decision-making, in agreement with the patient, taken in a multidisciplinary approach including neuroradiologist, neurosurgeon, radiotherapist and endocrinologist, is founded on the following:

- morphology: size, limits, relation to optic pathway, invasiveness toward cavernous sinus;
- pathology findings: immunohistochemistry, Ki67, p53, mitosis index;
- remnant progression;
- patient age and history and ability for prolonged regular surveillance;
- hypopituitarism;
- availability of and experience with the various adjuvant treatments in the center.

4.3. What are the options in case of recurrence or remnant progression?

4.3.1. Second surgery

Indications for reoperation of residual NFPA should take into account the initial surgical report and the size and location of the remnant.

Surgery is indicated for progressive remnant accessible to complete resection (limited by cavernous sinus invasion); for symptomatic optic pathway compression or to obtain 3–5 mm safety margins between superior tumoral dome and optic pathway for complementary RT; in case of progression after RT.

Surgery may also be initially planned as 2-step: intrasellar resection, followed by second surgery after the fall of the suprasellar contingent.

Remodeling of classical landmarks (sphenoidal rostrum, sphenoidal sinus septum) and poorer differentiation of intrasellar tissues may hinder surgery. Some teams recommend intraoperative neuronavigation in such cases, but this is controversial.

4.3.2. Radiation therapy

4.3.2.1. Pituitary radiation therapy techniques. Fractionated conformal RT delivers high-energy X photons, improving depth rendering and reducing radiation field penumbra. 3D location and dosimetry, multiple non-coplanar beams, intensity modulation and multi-slice fan-beam collimators have improved complex volume targeting, providing considerable progress. Total dose ranges between 45 and 50 Gy, fractionated in 25 sessions of 1.8–2 Gy [10].

Radiosurgery delivers radiation in a single session. The objective is to superimpose the target and the chosen reference isodose. The dose diminishes rapidly beyond the target, maximizing sparing of adjacent healthy structures. This requires an invasive stereotactic frame, to achieve precise positioning within 1 mm, a high-resolution imaging system, and 3D dosimetry. The devices used are the Gamma-Knife (201 Co^{60} sources on a hemisphere) and linear accelerator (LINAC). The marginal dose is usually 13–16 Gy in NFPA. This type of RT is feasible only if the target volume is clearly defined, small (<2–3 cm on the long axis) and sufficiently remote from the optic pathways to ensure <8 Gy irradiation of the chiasm and optic nerves.

Fractionated stereotactic RT associates the ballistic precision and multiple beam entries of radiosurgery to the principle of healthy tissue radioprotection by fractioning. The total dose is 45–50 Gy by 1.8–2 Gy fractions. CyberKnife is a miniaturized accelerator with a robotic arm, enabling hypofractionated stereotactic RT (3–9 sessions, depending on the team) with a non-invasive contention system based on the technical and dosimetric principles of radiosurgery.

Proton therapy is not widely available and thus little used for NFPA.

4.3.2.2. When is radiation therapy indicated in NFPA?. The efficacy of postoperative RT in NFPA is clearly undisputable, whatever the technique and whether treatment is first-line or post-surgical. The various types of RT show comparable efficacy in terms of tumoral control, and the choice between them depends on residue size, delineation and relation to adjacent neural structures, the particular center's technical experience and the patient's availability for follow-up [10].

Benefit, however, needs to be weighed against known side-effects, and especially RT-induced hypopituitarism, which is a frequent complication of all the RT techniques. Vascular complications and rare secondary brain tumors can be expected to be less frequent with hypofractionated or single-dose stereotactic RT, but follow-up is as yet too short for affirming that this is true.

Systematic postoperative RT is not indicated following complete resection, given the low rate of recurrence. In case of significant residual tumor, RT should be considered, taking account of risk factors for regrowth, patient age and history and presence of hypopituitarism. In most cases, the first-line attitude can be regular surveillance, postponing RT until recurrence is confirmed. First-line RT may be indicated in case of high growth potential and if the risk of hypopituitarism is no longer a major problem (notably, if the patient already displays hypopituitarism).

4.3.3. Medical treatment

The discovery of type D2 dopaminergic receptors and SST3 and SST2 somatostatin receptors within NFPAs, plus in vitro findings, have led to propose the use of dopamine agonists and somatostatin analogs in patients with NFPA. At present, none of these therapies has demonstrated sufficiently frequent significant efficacy in reducing tumor volume to be recommended systematically in case of failure of surgery.

Temozolomide is an oral alkylating agent that proved effective in pituitary carcinoma and aggressive adenoma (mainly

lactotroph or corticotroph). Low tumoral expression of O^6-methylguanine DNA methyltransferase (MGMT) is associated with good temozolomide response. Low expression of MGMT was shown to be more frequent in recurrent than non-recurrent NFPA, suggesting that temozolomide may also be useful as rescue therapy against very aggressive NFPA.

5. The particular case of non-functioning pituitary incidentaloma

Pituitary incidentaloma is a pituitary lesion discovered fortuitously on brain imaging (CT, MRI or PET) performed for some other reason.

When <10 mm on its longest axis, it is known as "pituitary microincidentaloma", and if >10 mm as "pituitary macroincidentaloma".

In the great majority of cases, fortuitous discovery leads to management that may differ from that of symptomatic pituitary adenoma. The following guidelines are founded on the literature data detailed in the article by Galland in the present Consensus document [14].

5.1. Initial assessment of microincidentaloma

5.1.1. Microincidentaloma

Microincidentaloma should undergo clinical assessment by an endocrinologist to screen for hormonal hypersecretion (signs of hyperprolactinemia, acromegaly or Cushing's syndrome) and any syndromic or familial context.

It should also undergo limited biochemical assessment: PRL and IGF-1 measurement (or overnight dexamethasone-suppression test if Cushing's disease is suspected). Screening for cortisol hypersecretion is reserved for clinical Cushing's syndrome. Screening for hypopituitarism is not recommended.

5.1.2. Ophthalmologic assessment

Ophthalmologic assessment is not recommended.

5.1.3. MRI

MRI centered on the pituitary gland should be performed if the imaging underlying discovery was not so centered.

5.2. Initial assessment of macroincidentaloma

Hormonal, neuroradiologic and visual assessment is similar to that performed in symptomatic non-functioning macroadenoma (see section 1 – Biochemical, neuroradiologic and clinical assesment of NFPA, above).

5.3. Management of non-functioning pituitary microincidentaloma

Attitude depends on microadenoma size.

5.3.1. Diameter of <5 mm

If the largest diameter is <5 mm, neither radiologic nor hormonal surveillance is recommended, and the attitude should be reassurance.

5.3.2. Diameter of ≥5 mm

If the largest diameter is ≥5 mm, initial control MRI is recommended, at 6 months for some teams and 12 months for others, repeated at 2 years to detect any progression. In case of non-progression, surveillance can be stopped. In rare cases of progression, annual MRI should guide management: continued surveillance, or surgery.

5.4. Management of non-functioning pituitary macroincidentaloma

Attitude again depends on macroadenoma size, and also on proximity to the optic chiasm.

5.4.1. Adenoma remote (we suggest ≥5 mm) from the optic chiasm

MRI at 1 year accompanied by hormonal biochemical assessment looking for hypopituitarism is recommended. In case of absence of progression, surveillance intervals may be lengthened to 2-yearly MRI. Annual hormonal biochemical assessment should be maintained in case of progression. Visual assessment (VA, VF) should be performed for lesions coming abutting the optic chiasm during follow-up. In case of progression, surgical resection may be considered.

5.4.2. Adenoma close to the chiasm

Surgery is not formally indicated but should be discussed with the patient, taking into account the natural history of NFPA and the low morbidity associated with surgery, and the need for the patient's compliance with surveillance, any plans for pregnancy, and risk factors for apoplexy, etc.

If surgery is not decided on, control MRI should be performed at 6 months, completed by hormonal and visual assessment. MRI and hormonal assessment are thereafter continued annually, with visual evaluation every 6 months.

In case of visual involvement, hypopituitarism or tumoral progression, treatment strategy is similar to that proposed for symptomatic NFPA (see section 2 – Surgical treatment of NFPA, above).

6. The particular case of pituitary apoplexy

Pituitary apoplexy is a serious acute complication of (usually non-functioning) pituitary adenoma, characterized by acute headache syndrome, possibly associated with visual disorder due to chiasmal compression or oculomotor involvement. In more than two-thirds of cases, it is associated with pituitary, and especially corticotroph, deficiency [15].

Historically, apoplexy was a systematic indication for surgery; the publication of reports of spontaneous clinical improvement, however, has led some authors to propose a more conservative attitude in some selected patients [16].

The issues in pituitary apoplexy are thus the following: should surgery be systematic or not? When should surgery be performed, if indicated?

In case of abstention, are high-dose corticosteroids useful?

6.1. Multidisciplinary management, including systematic medical treatment

6.1.1. Management of apoplexy

Management of apoplexy should be multidisciplinary: neurosurgeon, neuroradiologist, endocrinologist and ophthalmologist. Admission to a neurosurgery or endocrinology department in immediate proximity to a neurosurgery center is recommended.

6.1.2. Glucocorticoid treatment

As corticotroph deficit is almost always present, hydrocortisone replacement (if possible, after sampling for hormonal assay) should be initiated immediately; it is vital for the patient. It should, for example, consist of IV hydrocortisone hemisuccinate 50–100 mg every 8 hours, then followed by oral administration.

6.2. Indications for surgery in case of apoplexy

6.2.1. Surgery

Surgery is indicated in case of altered consciousness or recent or worsening severe visual defect.

In such cases, surgery should be performed as soon as possible, although an experienced pituitary surgeon may be preferred.

6.2.2. Isolated oculomotor palsy

Isolated oculomotor palsy is an indication for surgery according to some surgeons but not others.

6.3. Indications for conservative management (simple surveillance without immediate surgery)

6.3.1. Conservative management

Conservative management needs to be covered by high-dose IV or oral glucocorticoid treatment and clinical and ophthalmologic surveillance.

Conservative management is indicated in case of contraindications to surgery (unfavorable risk/benefit ratio).

Conservative management is indicated in case of stable or long-standing moderate visual defect.

Conservative management is indicated in case of isolated oculomotor palsy.

Conservative management is indicated on condition that change of strategy is feasible, with conversion to surgery in the absence of rapid improvement (within days).

6.4. Patients with pituitary macroadenoma close to the optic chiasm should be warned of the risk of apoplexy (clinical signs, at-risk situation)

6.4.1. Neuroradiologic evaluation in pituitary apoplexy

In acute-phase apoplexy (within the first hours after the beginning of signs and symptoms), CT is highly contributive to diagnosis in case of hemorrhage. MRI may prove non-contributive in case of hemorrhage in the acute phase (T1 and T2 isosignal).

After that very early phase, MRI is the imaging technique of choice.

7. Conclusion

NFPA are usually diagnosed in a context of signs and symptoms related to mass effect. Treatment, except in case of contraindication or particular situation, is thus basically surgical, after detailed hormonal, neuroradiologic and ophthalmologic assessment. Resection, generally via a trans-sphenoidal approach, needs to be performed by a neurosurgeon with large experience in pituitary surgery, to maximize the chances of complete resection and minimize complications. In case of remnant (frequent in large and often invasive adenomas), surveillance is required to avoid unnecessary adjuvant treatment (usually radiation therapy) in case of absence of growth. After complete resection, NFPA may recur in some patients. The attitude now recommended is also to propose surveillance to these patients, radiation therapy being proposed in case of growth of the relapsing tumor. Non-functioning pituitary incidentalomas may, because of their fortuitous discovery, require a different approach to symptomatic pituitary adenoma, especially when they are small or remote from the optic pathways.

Disclosure of interest

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

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