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Annales d'Endocrinologie 76 (2015) 201–209

Annales d'Endocrinologie
Annals of Endocrinology

Consensus

Biological and radiological exploration and management of non-functioning pituitary adenoma☆

Explorations et prise en charge des adénomes hypophysaires non fonctionnels : explorations biologiques et radiologiques

Gérald Raverot[a,b,*], Guillaume Assié[c,d], François Cotton[e,f], Muriel Cogne[g], Anne Boulin[h], Michèle Dherbomez[i,j], Jean François Bonneville[k], Catherine Massart[l,m]

[a] *Fédération d'endocrinologie, groupement hospitalier Est, hospices civils de Lyon, 69372 Lyon, France*
[b] *Inserm U1028, CNRS UMR5292, Lyon neuroscience research center, neuro-oncology and neuro-inflammation team, université Lyon-1, 69372 Lyon, France*
[c] *Center for rare adrenal diseases, department of endocrinology, hôpital Cochin, AP–HP, 75014 Paris, France*
[d] *Inserm U1016, institut Cochin, 75014 Paris, France*
[e] *Service de radiologie, groupement hospitalier Sud, hospices civils de Lyon, 165, chemin du Grand-Revoyet, 69495 Pierre-Bénite, France*
[f] *Inserm U630, CREATIS-LRMN, CNRS UMR 5220, université Lyon-1, 69621 Villeurbanne cedex, France*
[g] *Département d'endocrinologie, CHU, Saint-Pierre, Reunion*
[h] *Département de neuroradiologie, hôpital Foch, 92151 Suresnes, France*
[i] *Laboratoire de médecine nucléaire, centre de biologie-pathologie, CHRU de Lille, 59020 Lille, France*
[j] *Faculté de médecine, université Lille 2, 59045 Lille, France*
[k] *Université de Liège, CHU de Liège, domaine universitaire du Sart-Tilman, 4000 Liège, Belgium*
[l] *Unité fonctionnelle d'hormonologie, pôle biologie, CHU de Pontchaillou, rue Henri-Le-Guilloux, 35043 Rennes, France*
[m] *Inserm 1414, centre d'investigation clinique, université de Rennes 1, 35033 Rennes, France*

Abstract

Non-functioning pituitary adenoma may be totally asymptomatic and discovered "incidentally" during radiological examination for some other indication, or else induce tumoral signs with compression of the optic chiasm and pituitary dysfunction. Non-functioning adenomas are mainly gonadotroph, but may also be "silent". Treatment strategy depends on initial clinical, biological, ophthalmological and radiological findings. The present French Society of Endocrinology Consensus work-group sought to update the pitfalls associated with hormone assay and outline a hormonal exploration strategy for diagnosis and follow-up, without overlooking the particularities of silent adenoma. We also drew up basic rules for initial exploration and radiological follow-up of both operated and non-operated pituitary adenomas.

Keywords: Non-functioning pituitary adenoma; Pituitary gonadotroph tumor; Silent pituitary adenoma; Pituitary incidentaloma; Pituitary insufficiency

DOIs of original articles: http://dx.doi.org/10.1016/j.ando.2015.04.004,
http://dx.doi.org/10.1016/j.ando.2015.04.006,
http://dx.doi.org/10.1016/j.ando.2015.04.002,
http://dx.doi.org/10.1016/j.ando.2015.04.007,
http://dx.doi.org/10.1016/j.ando.2015.04.003
☆ Consensus of the French Endocrine Society: non-functioning pituitary adenoma.
* Corresponding author. Fédération d'Endocrinologie du Pole Est, 59, boulevard Pinel, 69677 Bron cedex, France.
E-mail address: gerald.raverot@chu-lyon.fr (G. Raverot).

http://dx.doi.org/10.1016/j.ando.2015.04.005
0003-4266/

Résumé

Les adénomes hypophysaires non fonctionnels peuvent être totalement asymptomatiques et découverts de manière « incidentelle » lors d'explorations radiologiques réalisées pour d'autres indications ou bien responsable de signes tumoraux avec compressions du chiasma optique et dysfonctions hypophysaires. Les adénomes non fonctionnels sont majoritairement des adénomes gonadotropes, mais il peut également s'agir d'adénomes dits « silencieux ». La stratégie thérapeutique de ces adénomes non fonctionnels dépend des données cliniques, biologiques, ophtalmologiques et radiologiques initiales. L'objectif de notre groupe de travail, dans le cadre du consensus de la Société française d'endocrinologie, a été de reprendre les pièges associés aux dosages hormonaux, de proposer une stratégie d'exploration hormonale au diagnostic et pour le suivi de ces adénomes, sans oublier d'identifier la particularité des adénomes « silencieux ». Nous proposons également des règles minimales pour l'exploration initiale et le suivi radiologique des adénomes opérés ou non.

Mots clés : Adénome hypophysaire non fonctionnel ; Adénomes hypophysaire gonadotrope ; Adénome hypophysaire silencieux ; Incidentalome hypophysaire ; Insuffisance antehypophysaire

1. Hormonal exploration: what technique for which assay?

1.1. Lactotrophs: prolactin assay

Prolactin is assayed by immunoanalysis using immunometric methods usually calibrated on the WHO 3rd International Standard 84/500. The techniques are made difficult essentially by the heterogeneity of circulating forms and by the "hook effect" [1,2].

1.2. Heterogeneity of circulating forms

Prolactin circulates in various forms: mainly active monomeric prolactin, but also heavy forms including macroprolactin, without biological action and mainly constituted by prolactin in complex with an immunoglobulin (Ig). At the present time, all the immunometric methods on the market recognize macroprolactin, but with varying intensity, leading to variable overestimation depending on the particular technique [3]. In case of moderately elevated prolactin contrasting with clinical presentation, the assay should be checked using a technique with little cross-reaction with macroprolactin. If the prolactin concentration is still elevated using an immunoassay with low cross-reactivity for heavy form, polyethylene glycol (PEG) precipitation should be considered to screen for macroprolactin if the method has been properly validated by the laboratory [1,4]. In case of positive macroprolactin screening, only gel-filtration chromatography can distinguish monomeric prolactin from heavy forms and correct the initial assay estimate.

1.3. Hook effect

In prolactinoma, prolactin concentration and adenoma volume are fairly well correlated. In case of moderate elevation despite large tumor size, an assay artifact known as the "hook effect" may be suspected. Here, an extremely high prolactin concentration saturates the tracer antibody sites before fixation to the detection antibody/prolactin complex, leading to underestimation. The classic solution to the hook effect problem is to perform the assay on a dilution of the serum sample. In case of very large macroadenoma on imaging, the clinician should therefore inform the biologist that assay should be performed on pure and on diluted serum.

1.4. Somatotrophs

1.4.1. GH assay

Immunometric GH assay should be performed on a serum sample collected in an anticoagulant-free tube [5]. The standardization of most methods following the recombinant human GH standard IS 98/574 allows results to be harmonized (1 μg = 3 IU) [6]. In exploring pituitary adenoma, GH can be measured on the oral glucose tolerance test, considered effective if the GH concentration falls below 0.4 μg/L (1.2 IU/L) and therefore requiring ultrasensitive techniques measuring low hormone concentrations. The methods on the markets now meet this requirement.

1.4.2. IGF-I assay

Determining IGF-I levels requires well-codified sampling in anticoagulant-free tubes, from a fasting patient to avoid variation with nutritional status [6]. Immunometric or competitive assay is performed on an acidified sample to release IGF-I and its carrier proteins, the sites of which are secondarily saturated by adding IGF-II. The first difficulty lies in calibration: results are calibrated on an international standard which for many years involved a poorly purified methionylated IGF-1 preparation (71 amino-acids) (WHO IRR 87/518) [7]. A new international standard of native IGF-I with 70 amino-acids (WHO IS 02/254) has been prepared and communicated to all relevant manufacturers [7]; to date, however, only two of the six suppliers respect this standard in their reagent packs.

The second pitfall lies in variations according, notably, to age, nutritional status, and hormonal status, whether physiological (thyroid hormones, insulin and estrogens varying over the menstrual cycle) or medication-related (replacement therapy at menopause). These variations require establishing reference values for each assay technique in a very large population with finely targeted inclusion criteria and stratified by age group in adults and pubertal stage in children [8–11].

1.5. Gonadotrophs

1.5.1. Gonadotropins

FSH and LH assay is generally performed by immunometry on automated immunoanalysis devices using antibodies that recognize beta-chain epitopes to exclude cross-reaction with other glycoproteins having an identical alpha sub-unit. These assays involve no particular difficulty, whatever the technique or serum concentration.

1.5.2. Testosterone

Testosterone assay in non-treated males is performed by immunoanalysis using competitive techniques assessing carrier protein-bound and physiologically active free testosterone. Probioqual external quality control showed good correlation for values greater than 4.8 nmol/L (1.4 ng/mL) between the various immunoanalysis methods on the market in 2007 and the gold standard of mass spectrometry coupled to liquid chromatography tandem mass (LC-MS/MS). Although these results are to be interpreted with caution as a matrix effect cannot be ruled out in samples reconstituted in buffered media that are not purely serous, they were validated in the 2010 French Society of Endocrinology guidelines [12]. Moreover, a very recent study confirmed the analytic performance of the devices currently on the market for total testosterone concentrations greater than 4 nmol/L (1.2 ng/mL), enabling eugonadism and hypogonadism to be clearly distinguished in adult males [13].

1.6. Corticotrophs

1.6.1. ACTH assay

The fragility of ACTH requires sampling with a tube (pink cap) containing EDTA with an added anti-protease, aprotinin. Centrifugation at exactly 4 °C and freezing should be performed within half an hour of blood-sampling. Also, the various immunometric assays on the market often lack sensitivity and are highly variable in the absence of any calibration standardization [14].

1.6.2. Cortisol assay

Serum cortisol is routinely assayed on competitive immunoanalysis. The 2006 French health products safety agency (AFSSAPS) report [15] required manufacturers to display the exactness of their method with respect to the gold standard LC-MS/MS and the functional detection limit locating the lower limit of measurement. Poor reproducibility and positive or negative biases with respect to LC-MS/MS in low concentration ranges (around 71 nmol/L or 29 ng/mL) were repeatedly noted in Probioqual reports. Thus, the low cortisol levels found with certain methods are to be interpreted with extreme caution, as exactitude and precision are mandatory in low concentration ranges if corticotroph insufficiency is to be detected for assessing the performance of the various dexamethasone suppression tests.

Urinary free cortisol is measured by competitive techniques, which may include an extraction phase to avoid cross-reaction with molecules of similar structure. Some techniques, however, are sufficiently specific to allow direct assay on non-extracted urine [16].

1.7. Thyrotrophs

1.7.1. TSH

TSH assay on immunometry should have the qualities of a third-generation assay: i.e., functional detection limit < 0.02 mIU/mL [17]. Although TSH reference values in Europe, taking all techniques together, are classically agreed to lie between 0.4 and 4 mIU/L, method-specific norms are recommended.

1.7.2. Free T4

Free serum T4 assay is performed by immunoanalysis using 1- or 2-step direct competition. Automated direct assay usually shows a negative bias due to equilibrium disturbance by serum dilution and sequestration of a certain amount of hormone by addition of antibodies, inducing underestimation [17]. Conversely, anti-T4 autoantibodies may lead to overestimation of free T4 concentrations on 1-step methods [17]. Standardization against the gold standard LC-MS/MS [18] should enable harmonization.

1.7.3. Alpha sub-unit assay

A single Immunoradiometric assay measures alpha sub-unit in serum or human plasma.

2. Interest of plasma assay of gonadotropins and their sub-units

2.1. Assessment of baseline secretion

In functioning adenoma, the hormone secretion rate is a reliable index of evolution. Persistent elevation signals incomplete resection even if no residue is visible on MRI. This important marker is generally absent in non-functioning adenoma [19].

The vast majority of clinically non-functioning pituitary adenomas (NFPAs) are gonadotroph, able to produce gonadotropins or their sub-units, as demonstrated on immunocytochemistry. However, elevated baseline plasma dimeric FSH and/or LH is rare. Elevated free sub-unit levels (mainly α, more rarely β-LH) are more common, but generally moderate.

When secretion is found, it is usually moderate and only exceptionally associated with specific clinical signs [20–23], hindering preoperative identification of gonadotroph adenoma, which is generally considered "silent" and diagnosed at onset on non-specific symptoms of tumoral syndrome (headache, visual disorder, pituitary deficiency) or on imaging assessment for some other indication ("incidentaloma": cf. dedicated article).

When baseline plasma concentrations of dimeric FSH, dimeric LH or free α sub-unit are carefully interpreted, it is found that half of male gonadotroph adenoma patients (as subsequently confirmed on immunocytochemistry or in vitro tumor secretion analysis) show excess secretion of FSH, LH or their free sub-units in quantities sufficient for plasma assay [24–28].

In pre-menopausal women, this is less common (about 30% of cases); after the menopause, it is much harder to assess

the "functioning" or "silent" status of gonadotroph adenoma, given the physiological elevation of gonadotropins and their sub-units in women of this age. For example, FSH and LH levels were studied in 112 gonadotroph adenoma patients; 48% of male patients and 25% of women under 50 years of age showed gonadotropin elevation, while serum concentrations in post-menopausal women were within normal limits [29].

Finally, even when initially elevated, β-LH sub-unit assay is not predictive of residual tumor or recurrence or progression of an existing residuum at follow-up [30].

2.2. Dynamic assessment of gonadotropin secretion

2.2.1. GnRH stimulation

Elevated FSH and LH after GnRH stimulation was reported in respectively 75% and 50% of cases of pituitary adenoma [31]. There is, however, no consensus as to normal GnRH test response. Moreover, response varies over the menstrual cycle, and is non-specific, being found in other types of pituitary adenoma, notably prolactinoma [24,25,32,33].

2.2.2. TRH stimulation

In case of baseline FSH hypersecretion, TRH stimulates FSH production in 60–70% of cases, whereas in baseline LH hypersecretion, there is paradoxical LH response to TRH in only 20–30% of gonadotroph adenomas, with paradoxical LH α or free ß sub-unit response in 60% of cases.

If there is no baseline elevation of gonadotropins or sub-units, paradoxical TRH stimulation response is rare.

As with the GnRH test, non-specific stimulation may be found in other types of adenoma [24,26,27,30,34–36].

Thus, the TRH test does not confirm diagnosis of gonadotroph adenoma; nor is it a sufficient predictive marker of tumor residuum or early recurrence during follow-up [19,30].

2.2.3. Risks of dynamic tests

As well as being non-contributive, dynamic GnRH and TRH tests are not risk-free, associated pituitary apoplexy having been reported [37–40]. However rare, the potential severity of such a complication, added to the lack of real benefit, means that these tests should not be performed.

2.3. Another marker: chromogranin A

Chromogranin A elevation may be found in certain pituitary adenomas [41], but assay has been shown to be of no value in diagnosis or in follow-up [42,43].

3. Is exploration for silent pituitary adenoma useful?

Certain NFPAs are positive on immunohistochemistry for one or more pituitary hormones. These are known as "silent" adenomas. The most frequent is gonadotroph adenoma, which will not be dealt with here. Others, more rare, are corticotroph, somatotroph or thyrotroph. Can these be identified preoperatively, ahead of immunohistochemistry?

3.1. Hormonal exploration of silent corticotroph adenoma

3.1.1. Free urinary cortisol, cortisol cycle, dexamethasone suppression test: is silent corticotroph adenoma really silent?

Are all corticotroph adenomas silent if they do not show clinical signs of hypercortisolism? Such at least is the definition applied in most studies on this topic [44–54]. But can we be sure that these adenomas are not in fact associated with slight but real abnormalities of the corticotroph axis, or in certain cases that Cushing's disease has not simply been overlooked? There have been no large series systematically looking for signs of slight hypercortisolism associated with silent corticotroph pituitary macroadenoma. Out of 2 patients with clinically silent corticotroph adenoma, Sahli et al. reported 1 as having incomplete dexamethasone suppression [55]. Out of 27 patients with silent corticotroph macroadenoma, Webb et al. reported normal free urinary cortisol in both of the 2 patients tested, but they had been tested precisely because of the high plasma cortisol levels randomly sampled during the day [56]. There is likely a continuum of secretion between secreting and less secreting forms of corticotroph adenoma [52,57], as in infraclinical adrenal Cushing's syndrome [58]. What proportion of so-called "silent" corticotroph adenomas are truly silent? We do not know.

Absence of clinical hypercortisolism at a given moment is no guarantee against hypercortisolism to come. There have in fact been several reports of clinically silent adenomas that progressed toward definite hypercortisolism [59–63]. May not some of these be forms of cyclic hypercortisolism? Reports of macroadenoma with cyclic Cushing's syndrome are, at any rate, few and far between! Prevalence of such definite hypercortisolism occurring during follow-up is unknown but would seem to be low, at around 2 per 500 pituitary adenomas [59].

Perhaps corticotroph macroadenoma may be silenced by apoplexy. Sahin et al. published one such case report [64]. Moreover, in series of silent corticotroph adenoma, apoplexy is a frequent presenting symptom [50,53], with a prevalence of 9 out of 27 cases reported by Webb et al. [56] and 6 out of 24 cases reported by Cho et al. [65]. Preoperative hormonal exploration, if it had been performed, would probably have revealed corticotroph insufficiency, although this is not incompatible with possible hypercortisolism predating the apoplexy. Once again, hormonal work-out, ruling out clinical hypercortisolism, is the criterion establishing the silent nature of an adenoma.

Finally, silent corticotroph adenoma frequently conserves a functional corticotroph axis despite deficits in one or more pituitary function [47,53], and this is probably fairly specific to corticotroph adenoma, especially in case of slight abnormalities suggestive of hypercortisolism. However, this remains to be assessed.

3.1.2. Elevated morning plasma ACTH

Several studies reported elevated plasma ACTH measured at 8 a.m. in certain cases of silent corticotroph adenoma [48–53,56]. The proportions of patients with elevated ACTH varied from 10% to 100%. The degree of elevation was also variable: usually moderate (1 to 2-fold the normal values),

but sometimes high (6-fold the normal values). Despite ACTH elevation, the corresponding plasma cortisol level showed no increase.

Other studies reported no increase in ACTH level [44]. Two studies compared 8 a.m. ACTH in silent corticotroph adenoma versus patients with other types of non-functioning adenoma [65,66]. ACTH levels were similar in both series, and both reported ACTH elevation in certain cases. These studies raise the question of the significance of 8 a.m. ACTH elevation in silent corticotroph adenoma. The data would seem to show that the ACTH threshold corresponding to these adenomas is low.

3.1.3. Dynamic tests

Some studies reported ACTH and cortisol response to CRH in silent corticotroph adenoma. Tateno et al. found a clear increase in ACTH levels with CRH (by a factor of 6 ± 4.1), although this was not very different from the response observed in other types of non-functioning adenoma (factor of 4 ± 2.9) [67]. Cortisol elevation was similar in both groups. Kojima et al. reported ACTH elevation after CRH stimulation [49]. From these sparse data, it would seem that CRH response is fairly non-specific in non-functioning corticotroph adenoma.

ACTH levels were assessed under dexamethasone [67]. Following 0.5 mg dexamethasone at midnight, ACTH levels were slightly higher in the silent corticotroph adenoma group (13 ± 6.9 pg/mL) compared to other types of non-functioning adenoma (7 ± 1.7 pg/mL), but the difference was not significant.

Finally, 1 case of paradoxical ACTH response to TRH and LHRH has been reported [51].

3.1.4. Abnormal forms of ACTH

Several groups have identified abnormal ACTH [68–70] in silent corticotroph adenoma, in the form of large size precursors, corresponding to abnormal maturation of proopiomelanocortin (POMC). These high-molecular-weight forms seem not to show the biological activity of ACTH, thus explaining in some cases the absence of hypercortisolism despite elevated ACTH. Screening for such ACTH maturation abnormalities in non-functioning adenoma, however, cannot yet be recommended, above all due to the lack of standardization of such exploration.

3.2. Hormonal exploration of silent somatotroph adenoma

3.2.1. Is silent somatotroph adenoma really silent?

In published series and case reports, IGF-1 (and/or GH) assay is most frequently used for apparently non-functioning pituitary adenoma. It is therefore rare for a somatotroph adenoma to be judged "silent" without hormonal support for the diagnosis, unlike in the case of silent corticotroph adenoma, so described purely on the basis of clinical aspect. The value of this minimal exploration, however, is to be weighed against problems of assay technique, sampling procedure (single or multiple site GH sampling? oral glucose tolerance test?) and choice of normal values, notably with respect to age, which may all strongly influence interpretation [8,71].

The major issue in silent somatotroph adenoma is the possible discordance between absence of clinical signs of acromegaly and moderate elevation of IGF-1 or GH. In a consecutive series of 100 operated pituitary tumors, Wade et al. identified 24 somatotroph adenomas on immunohistochemistry, including 11 with clear acromegaly, 4 with slight acromegaly, 8 without acromegaly but with elevated IGF-1, and only 1 with neither acromegaly or IGF-1 elevation [72]. In a series of 17 patients, Trouillas et al. reported 4 patients with slightly elevated GH levels and 13 with normal levels (< 5 ng/mL). In a series of 9 patients, Pagesy et al. included patients with moderate IGF-1 elevation but normal GH levels [73]; certain patients nevertheless showed clinical signs of acromegaly, although discrete for some. Other case reports and series found patients without clinical acromegaly but with variable moderate concomitant IGF-1 and GH elevation [74–76] or normal IGF-1 levels [77,78].

Will such infraclinical somatotroph adenomas become more highly secreting? Will persistent moderate GH hypersecretion end up by inducing signs of acromegaly? There are no clear answers. Sakharova et al. reported the case of a female patient at 8 years' follow-up, with slightly elevated IGF-1 and no signs of acromegaly [75].

3.2.2. Is IGF-1 assay enough?

Is IGF-1 assay enough, or should GH assay be associated? Thirty percent of cases of acromegaly show discordance between IGF-1 and GH levels, but it is usually IGF-1 that is elevated and GH normal [71]. Certain situations are known to lower IGF-1 levels: denutrition, kidney failure, liver failure, oral estrogen therapy, hypothyroidism and uncontrolled diabetes [71]. Normal IGF-1 findings in such situations are therefore to be interpreted with caution.

Specifically in clinically silent somatotroph adenoma, Kalavalapalli reported 3 cases of discordance, with normal IGF-1 and elevated GH levels [79]. Naritaka et al. reported a case of slightly elevated GH with normal IGF-1 level, out of 3 cases with concomitant IGF-1 and GH assay [78]. Matsuno et al. reported 3 cases of silent somatotroph adenoma, all associating normal GH and IGF-1 levels [80]. Klibanski et al. reported 1 case (out of 3) with normal IGF-1 but elevated GH levels [74]. Prevalence of normal GH and IGF-1 levels is probably biased by variations in the definition of "silent".

3.2.3. GH assay after oral glucose tolerance test

The GH nadir after oral glucose tolerance test (OGTT) seems to be remarkably sensitive in diagnosing infraclinical somatotroph adenoma, most studies reporting abnormal suppression. In a series of 3 silent somatotroph adenomas (2 with slightly elevated IGF-1), Klibanski et al. found elevated GH in all cases, not showing sufficient suppression under OGTT [74]. Pagesy et al. included 9 patients with normal GH levels (< 5 ng/mL) but no suppression on OGTT [73]; IGF-1 was moderately elevated. Finally, Sakharova et al. reported insufficient GH suppression on OGTT in all 3 of their patients [75]; again, IGF-1 was moderately elevated.

3.2.4. Other hormonal tests

There are just a few data for GH response to TRH and GnRH. Paradoxical responses have been reported [78,80]. However, these data are insufficient to prove the contribution of these tests.

4. Interest of screening for pituitary deficiency: frequency and minimum assessment

4.1. Frequency of preoperative pituitary deficiency

In macroadenoma, the frequency of pituitary deficiency at diagnosis varies between series, but with deficiency in at least one axis in 60–85% of cases.

The most frequent deficit is in gonadotropin, found in more than 80% of cases, compared to 20–50% for thyrotropin and corticotropin [19,81–83]. Most studies did not assess somatotropin deficiency dynamically, but it may concern almost 70% of cases [82].

Data are scarce for non-functioning pituitary microadenoma [84,85], but it is known not to be complicated by pituitary deficiency, which does not need to be investigated [86,87].

4.2. Exploration of preoperative pituitary deficiency

Only the corticotroph axis should undergo dynamic exploration at diagnosis of non-functioning pituitary macroadenoma. Although very low 8 a.m. cortisol levels indicate pituitary deficiency, a short synacthen test or insulin tolerance test, depending on general health status, is recommended.

The thyrotroph axis should undergo static exploration, with 3rd generation TSH assay and free T4 assay.

For the gonadotroph sector, no biological exploration is required in women with spontaneously normal menstrual cycle; in case of amenorrhea, on the other hand, even in women of menopausal age, FSH assay can guide diagnosis toward a peripheral etiology or else gonadotropin deficiency.

In male subjects, LH, FSH and plasma total testosterone should be assayed to screen for associated gonadotroph deficiency.

We have no clinical data relating to the interest of preoperative screening for somatotroph deficiency.

4.3. Interest of screening for pituitary deficiency

Preoperative screening for pituitary deficiency enables adapted replacement therapy to be initiated to improve general health status ahead of surgery and avoid intraoperative acute corticotroph deficiency.

The peri-operative corticotroph replacement protocol may be guided by a deficit detected preoperatively. In case of preoperatively proven corticotroph deficiency, 48 hours' supraphysiological corticotherapy should be administered perioperatively (e.g., hydrocortisone, 50 mg every 8 hours on D0, then 25 mg every 8 hours on D1, and 25 mg at 8 a.m. on D2). In case of intact preoperative corticotroph function and if selective adenoma resection is feasible, peri-operative glucocorticoids are unnecessary [88].

Moreover, knowledge of preoperative pituitary deficiency can influence treatment options. Pituitary adenoma resection improves pituitary function in 30% of cases and achieves normalization in 20%, with only 1% of aggravation and unchanged function in 50% [81–83]. Surgery may thus be indicated in young patients even in the absence of visual disorder, and especially in women hoping for pregnancy (see article on Incidentaloma).

4.4. Postoperative follow-up of pituitary function

In the immediate (7–10 days) postoperative period, the focus should be on the assessment and correction of corticotroph pituitary deficiency and on screening for diabetes insipidus.

The corticotroph axis recovers very quickly postoperatively, and serum cortisol assay at 8 a.m. 3–7 days after surgery identifies patients who have recovered normal corticotroph function. Thus, cortisol < 100 nmol/L suggests presence and > 450 nmol/L absence of corticotroph deficiency; intermediate findings require complementary tests. The short synacthen test is not reliable at these early stages; only the insulin tolerance test shows 100% sensitivity and specificity, but is often precluded by general health status, although it remains the test of choice, often performed 4–6 weeks after surgery, with minimal corticotroph replacement (15–20 mg per day) in the meanwhile [88].

An alternative may be to systematically perform dynamic exploration 4–6 weeks post-surgery, reducing hospital stay and facilitating practical organization in certain centers [89]. Moreover, it identifies patients with delayed corticotroph axis recovery [88].

The literature data suggest that corticotroph deficiency may resolve within 3 months of surgery [90,91]; it is therefore recommended to repeat corticotroph axis exploration at 3 months in case of initial deficiency [88].

Likewise, the thyrotroph and gonadotroph axes should be assessed during the postoperative period. However, there are few data indicating the ideal frequency and timing for such exploration. Although systematically performed 4–6 weeks after surgery, long-term predictive value is unknown. In case of initial deficiency, it is therefore recommended to repeat exploration at 3, 6 and 12 months [19].

In the absence of postoperative pituitary deficiency, there are no data supporting exploration for secondary onset in the absence of residual tumor; in case of tumoral recurrence or residual tumor progression, on the other hand, further pituitary exploration is recommended, similar to that performed at initial diagnosis, to screen for onset of deficiency, to be repeated at least once yearly in the absence of complementary treatment [81].

In case of complementary radiation therapy, pituitary function exploration should be systematic, at least once yearly for at least 10 years, due to the increased risk of onset of deficiency during follow-up [19,81].

5. What neuroradiological exploration?

Positive diagnosis is based on MRI, which is the reference examination for the sellar region. Gadolinium injection should be associated. The usual contraindications (pregnancy, pacemaker, etc.) are to be respected.

5.1. Types of acquisition

Coronal acquisitions should be taken perpendicular to the bicallosal plane. MRI should comprise at least:

- sagittal spin-echo (SE) T1-weighted, coronal T1 and T2-weighted sequences and a gadolinium-enhanced (or, ideally volumetric gadolinium-enhanced with coronal reconstruction and lesion volume assessment) T1-SE acquisition;
- thin slices (≤ 3 mm) with elevated matrix;
- complementary sequences according to the circumstances: dynamic, axial T1-SE fat-sat, high-resolution coronal COR T1-SE, high-resolution coronal SAG T1-SE.

Secondary CT-scan without contrast enhancement may assess skull-base lesions or explore possible tumoral calcification in differential diagnosis.

5.2. MRI results

In macroadenoma, MRI finds a mass centered on the sella turcica, which is enlarged, with T1/T2 signal varying according to necrotic and/or hemorrhagic areas, and possible fluid level. Uptake is usually not intense and less than in the healthy anterior pituitary parenchyma. Multiple microcysts on T2-weighted sequences suggest silent corticotroph adenoma [92].

Extension should be assessed:

- superior extension toward the optic pathways: treatment depending mainly on visual disorder, the relation between the superior pole of the tumor and the optic chiasm should be carefully assessed (chiasmal displacement or compression, hypersignal on T2);
- lateral extension into the cavernous sinus, assessing percentage internal carotid enclosure (caliber being generally conserved), aspect of the medial venous plexus of the cavernous sinus and visualization of the medial wall on 3T MRI; the Knops classification may be used: extension beyond the lateral intercarotid line showing 95% predictive value for cavernous sinus invasion;
- inferior extension in the sphenoidal sinus, with sellar floor analysis;
- posterior extension, with clivus analysis.

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

Differential diagnosis is dealt with in the article on incidentaloma.

Diagnosis is mainly based on sella tunica size, degree of tumor uptake, presence of calcification, and presence of intralesional fluid level.

Imaging follow-up, after surgery, in case of severe or progressive visual disorder.

In case of immediate postoperative aggravation, CT without enhancement explores for surgery-site edema.

Early MRI in the first postoperative days or weeks is reserved for complications (e.g., rhinorrhea). MRI detects cerebrospinal fluid leakage in slightly more than 75% of cases [93,94], on specific highly T2-weighted high-resolution coronal slices of at least 2 mm, ideally on 3T MRI.

In classical postoperative surveillance programs, MRI is always performed according to the same protocol (the same as the initial protocol), ideally on the same machine or with data integrated into the institution's picture-archiving and communication system (PACS) at month 3 and 12 and then yearly.

In simple surveillance, yearly MRI follows the initial protocol, with comparison of lesion volume. It is often useful to compare all examinations rather than only the last two, as tumor growth is usually minimal.

Disclosure of interest

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

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