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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

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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

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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].