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Non-functioning pituitary macro-incidentalomas benefit from early surgery before becoming symptomatic

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ABSTRACT

Objective: Pituitary incidentalomas (PIs) constitute an increasingly clinical problem. While the therapeutic management is well defined for symptomatic non-functioning PIs (NFPIs), a controversy still exists for asymptomatic macro-NFPIs between surgery and a "wait and see" approach. The aim of this study is to compare surgical results between symptomatic and asymptomatic macro-NFPIs.
Methods: We conducted a retrospective study on 76 patients with newly diagnosed symptomatic and asymptomatic macro-NFPIs operated on between 2001 and 2010. We compared age, tumor size and surgical results between these two patient groups.
Results: After the initial evaluation, 48 patients were found to be symptomatic. Gross total removal (GTR) rate was significantly higher in asymptomatic (82%) than in symptomatic patients (58%; $p = 0.03$). Gross total removal was strongly associated with Knosp's classification ($p = 0.01$). Postoperative endocrinological impairment was significantly associated with the existence of preoperative symptoms ($p = 0.03$). It was 10 times less frequent in the asymptomatic group. In symptomatic patients, postoperative visual and endocrinological impairment were present in 49% and 78% versus 0% and 14% in asymptomatic patients respectively.
Conclusions: The endocrinological and visual outcome was better in those patients who underwent surgery for asymptomatic tumors. The extent of tumor resection was also significantly greater in smaller tumors. It would therefore be appropriate to offer surgery to patients with asymptomatic macro-NFPIs.

1. Introduction

Recent guidelines define pituitary incidentalomas (PIs) as previously unsuspected pituitary lesions incidentally discovered on brain imaging performed for an unrelated reason [1]. With the advent of modern neuroimaging in the last 30 years, more patients undergo computed tomography and magnetic resonance imaging (MRI) and PIs constitute an increasingly common clinical problem. The estimated prevalence of PIs ranges from 1.5% to 31% [2–6] and from 10% to 38.5% in autopsy findings and imaging studies respectively [7–9]. Pituitary incidentalomas are most often micro-adenomas, and macro-adenomas are found in only 0.16–0.20% of the cases [10,11]. Most PIs are hormonally inactive. These non-functioning PIs (NFPIs) often are immunopositive for gonadotropins and named gonadotropin [12] or null cell adenomas [13]. Some of them are immunopositive for adrenocorticotropic hormone (ACTH) or growth hormone (GH) or prolactin (PRL) and are thus called silent adenomas. According to recent guidelines [1], surgery is recommended for NFPIs when visual and/or endocrinological impairment is discovered by ophthalmologic or pituitary function evaluation. In contrast, the guidelines for the management

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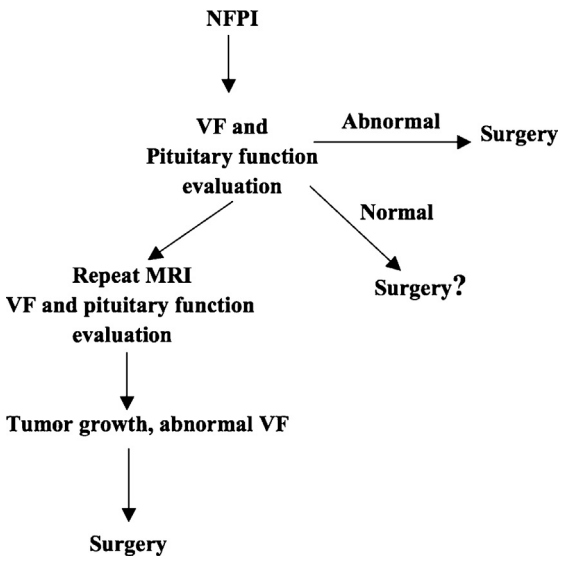

Fig. 1. Evaluation and treatment of non-functioning pituitary macro-incidentalomas. VF: visual field; NFPI: non-functioning pituitary incidentalomas. Modified from Freda et al. [1].

of macro-NFPIs without any symptoms are controversial (Fig. 1): some authors recommending surgery [14–16] while others favor a "wait and see" approach mandating regular radiological evaluation to document tumor progression [1,17,18]. However, in our knowledge, there is no study on the evaluation of surgery for asymptomatic macro-NFPIs.

In this study, we raise the question of the utility of surgery in asymptomatic macro-NFPIs. To do this, we compared the surgical results of two groups of patients: symptomatic and asymptomatic, after preoperative evaluation in a series of 76 macro-NFPIs. We present some arguments in this multidisciplinary debate to aid endocrinologists and neurosurgeons in their choice of management.

2. Materials and methods

This retrospective study was based on the results of 3 experienced neurosurgical teams at Groupement Hospitalier Est, Lyon, France (GP, EJ), and Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (RTD) and Christian Medical College, Vellore, India (AGC, RTD). The patients were operated on from 2005 to 2010 in Lyon and Vellore and between 2001 and 2010 in Lausanne.

The neurosurgeons concerned by this multidisciplinary study were experienced and had performed at least 300 transsphenoidal surgeries before inclusion. In these 3 centers, the diagnostic procedure as well as the endocrinological and ophthalmological assessments were strictly the same as described below. Besides, in order to be certain of the homogeneity of our 3 centers, we first compared results of the 3 centers in terms of all patients' characteristics including age, sex, reasons for imaging, preoperative MRI findings, quality of resection, postoperative morbidity, endocrinological and ophthalmological results. There was no significant difference ($p > 0.05$) in all these parameters between the centers. As consequences, we presented pooled results.

2.1. Inclusion criteria

All the patients presented with a macro-NFPI, defined as a pituitary tumor incidentally discovered on neuroimaging (computed tomography scan or MRI) for evaluation of an unrelated disease [1]. The diagnosis of NFPI was made on clinical, biochemical and histopathological criteria. Those patients with symptoms of hypopituitarism or hyperfunctioning of the pituitary gland were excluded. All the tumors were studied by routine histological techniques and immunocytochemistry. Only gonadotropin adenomas immunostained for FSH/LH or immunonegative for all the antibodies against the pituitary hormones were included [12,13]. The GH, PRL and ACTH silent adenomas were also included. Authors have chosen to only include pituitary adenoma because others type of incidentalomas such as cyst are not enough progressive to engender symptoms without therapy.

2.2. Intervention

All patients underwent transsphenoidal surgery for adenoma removal. The procedures used were the fully endoscopic endonasal approach [19] or the traditional transsphenoidal approach [20].

2.2.1. Neuroimaging evaluation

All patients were preoperatively evaluated by the same imaging protocol, which included systematic 3D T1-weighted sequences with and without contrast injection and a 3D T2 sequence. Characteristics (volume: (height × length × width)/2, height and cavernous sinus invasion) of tumors were collected using coronal T2 and 3D T1 weighted MR imaging with and without contrast injection. For cavernous sinus invasion, the Knosp's classification was used [21]. If the grading was different between the 2 cavernous sinuses for any patient, the tumor was classified according to the higher grade.

At 12 months following surgery and annually thereafter, all patients underwent postoperative control MR imaging with the same sequences as those performed preoperatively. Senior pituitary surgeons and independent neuroradiologists in each center judged the quality of resection based on the 12-month postoperative imaging in order to avoid any artifacts. The resection was classified as gross total (GTR) or subtotal removal (STR).

2.2.2. Endocrinological evaluation

Preoperatively, all patients were assessed with static and/or dynamic endocrinological tests to evaluate anterior pituitary functions. Hormonal deficiencies were assessed by investigation for LH/FSH, ACTH and TSH deficiencies. TSH deficiency was defined as a low or "inappropriately normal' TSH and free T4 levels below the normal references values. LH/FSH deficiency was defined as a low or 'inappropriately normal' LH/FSH levels combined with low serum oestradiol in menopausal women and with serum testosterone below the reference values in adult men. ACTH deficiency was defined as a peak cortisol < 550 nmol/l in the short synacthen (250 μg) or the insulin tolerance test or as a random morning serum cortisol value < 100 nmol/l in the absence of steroid therapy. Patients were classified thus: as having normal function, at least one pituitary hormone deficiency or panhypopituitarism.

After surgery, patients' conditions were assessed by the same endocrinological tests and were classified as having normalized if all the pituitary axes recovered, improved or worsened when one or more pituitary axis recovered or failed respectively, and, stable if no change occurred.

The postoperative endocrinological status was considered at the 12-month follow-up.

2.2.3. Ophthalmologic evaluation

Before surgery, all patients underwent a complete ophthalmological examination of visual acuity (VA) and visual field (VF). Visual acuity was considered normal at 20/10. Visual fields were tested with an automatic perimeter. A mean deviation of 1 decibel (dB) for the affected eye was considered as significant. Patients were