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Original Article

Non-functioning pituitary adenoma underwent surgery: A multicenter retrospective study over the last four decades (1977–2015)

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ABSTRACT

Objective: To assess clinical features, diagnostic procedures, therapies and outcomes in patients with clinically non-functioning pituitary adenomas (NFPAs) surgically treated over the last four decades.
Design and methods: A multicenter retrospective study in NFPA patients periodically followed up in specialized neuroendocrinology units who underwent surgery in the period 1977–2015 was performed.
Results: A total of 131 patients were studied [66 women (50.4%); mean age 52.6 ± 14.8 years (range, 15–82)]. Median diameter of the adenoma was 2.6 cm (interquartile range, 2.0–3.1). The most frequently type of surgery used was endoscopic endonasal surgery (58.5%) followed by microscopic transsphenoidal surgery (37.4%). Radiation therapy was used in 19 patients (14.5%). Ki-67 labeling index performed in 54 patients was ≤2% in 70% samples. After a median follow-up time of 57 months (25 to 128 months), tumor diameter significantly decreased to 0.9 cm (0–1.8 cm), $p < 0.001$. Multivariant analysis showed that endoscopic endonasal surgery (HR 2.74, 1.06–6.87, $p = 0.036$) and radiotherapy (HR 0.04, 0.02–0.65, $p = 0.024$) behaved as positive and negative predictors, respectively, of tumor absence in the follow-up. Endoscopic endonasal surgery (HR 6.71, 1.45–31.05, $p = 0.015$) was the only positive predictor for complete cure in the follow-up.
Conclusion: NFPAs surgically treated in Spain are usually macroadenomas diagnosed around the sixth decade of life with no sex predilection. Type of surgery is associated with clinical outcome. Endoscopic endonasal surgery behaves as a positive predictor for the absence of tumor imaging and complete cure in the follow up.

1. Introduction

Today, pituitary adenoma (PA) is the third leading cause of intracranial neoplasia, following to meningioma and glioma [1–4]. According to some surveys, its incidence has almost doubled over a period of 30 years, from 6 to 11 cases per million inhabitants/year [5], with a clinical prevalence around 1 case per 1000 inhabitants in recent studies [6]. The prevalence of PA in imaging studies is around 22.5%, with wide range (1–40%); while in autopsy studies is 14.4% (range 1–35%) [1].

PA can be functioning and nonfunctioning, according to the presence or absence of hormonal hypersecretion. The main types of PA are clinically non-functioning pituitary adenomas (NFPAs), prolactinomas, growth hormone (GH) secreting adenomas or somatotropinomas and corticotropin (ACTH) secreting adenomas or corticotropinomas. The frequency of the different types of PA is different and varies with age. While prolactinomas are the most common PA in young patients (2nd-4th decade of life), from age 40, the most prevalent are NFPAs [7].

NFPAs constitute about a third of all PA and its incidence has been estimated at 1.79/100,000 inhabitants/year [8]. Its prevalence is around 26–90 cases per million and constitute 50% of pituitary tumors in large surgical series [8,9]. In clinical series its prevalence is much greater around 400 per million [6].

NFPAs are the pituitary macroadenomas (≥1 cm) more frequent in adults and include primarily gonadotropinomas, which produce, although most of them do not secrete, gonadotropins or their subunits (mainly subunit alpha) followed by null cell adenomas, and finally other silent PA, such as corticotropinomas, somatotropinomas, and prolactinoma. Depending on the size, these tumors may be symptomatic or not. Macro-NFPAs are accompanied by considerable morbidity, usually associated with tumor mass effect causing neuro-ophthalmological symptoms and pituitary hormonal failure. On the contrary, micro-NFPAs (<1 cm) are usually asymptomatic incidental findings on imaging studies. Treatment of choice is transsphenoidal surgery in symptomatic cases with the use or not of adjuvant radiotherapy in the

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case of persistent or recurrent disease, and periodic observation in asymptomatic tumors [10–14].

NFPAs series published to date in our country are scarce and have been usually performed in a small number (~30–50) of patients from a single hospital and with a short follow-up [15–17]. On the other hand, efficacy and surgical outcomes of the different surgical techniques in these tumors have not been clearly conclusive. In the present study we retrospectively reviewed the clinical characteristics, treatments used, pathological findings and clinical outcome of a large cohort of patients with NFPAs surgically treated in the last four decades in three Spanish tertiary hospitals. The main objectives were to study the relationship between different surgical techniques (microscopic and endoscopic) with absence of tumor and complete cure (absence of tumor and adenohypophysis normofunction) in the last medical visit.

2. Patients and methods

2.1. Patients

A retrospective multicenter study of NFPAs underwent surgery between 1977 and 2015 in the Endocrinology department of three Spanish hospitals (Hospital Universitario Ramón y Cajal, Madrid; Complejo Hospitalario Universitario de A Coruña, A Coruña; and Hospital Universitario de Bellvitge, Barcelona) was performed. All registered cases of NFPA in each Endocrinology department during the study period were analyzed and all clinical records of the patients who underwent surgery were reviewed.

Inclusion criteria were the histological demonstration of the tumor and the absence of clinical symptoms compatible with pituitary hyperfunction. For homogeneity, MEN 1 patients ($n = 2$) were excluded from the study. Patient percent distribution according to different hospitals included was: Hospital Ramón y Cajal, Madrid, $n = 54$ (41.2%); Hospital Universitario A Coruña, $n = 42$ (32.1%); and Hospital de Bellvitge, $n = 35$ (26.7%). Median follow-up was 57 months (interquartile range, 25 to 128 months).

2.2. Methods

In every patient the following clinical parameters were recorded: age at diagnosis, personal and family history, drugs at the time of diagnosis, association or not with multiple endocrine neoplasia, main complaint at consultation, neuro-ophthalmological and endocrinological signs and symptoms and serum baseline hormonal determinations (PRL, GH, IGF-1, ACTH, cortisol, TSH, free T4, FSH, LH, estradiol in women and testosterone in men). The presence of hypopituitarism (partial or complete), number of axes involved, the presence of diabetes insipidus, and hyperprolactinemia was registered. Imaging study at diagnosis and the degree of visual impairment were also evaluated.

Date of surgery, type and surgery technique, and surgical complications were recorded. Histopathological and immunohistochemical study of NFPAs was investigated. Lastly, after surgery, each patient was assessed on his/her last clinical visit analyzing clinical and laboratory data, the need of medical therapy and/or radiotherapy, tumor persistence/recurrence or clinical cure (absence of pituitary tumor in imaging study and normal pituitary function).

2.3. Statistical analysis

For quantitative variables, results are expressed as mean ± SD for normally distributed data, (age) and as median (interquartile range) for nonparametric data (time of follow-up and maximal tumor diameter). Adjustment to normal distribution was tested by the Kolmogorov test. Categorical variables are described as percentages. For comparisons of means between two groups of patients the Student *t*-test was used for normally distributed data (age), and the Mann-Whitney test to compare the medians of two different groups of patients (comparison of maximal tumor diameter in patients with and without hypopituitarism both before and after surgery). Willcoxon test was used to compare the medians for nonparametric data in the same group of patients (comparison of maximal tumor diameter at diagnosis and at last clinical visit). For categorical comparisons the χ^2 test (evaluation of sex, age groups at diagnosis, persistence of tumor at last visit, tumor size group, Ki 67 value group, hyperprolactinemia, complete and partial hypopituitarism, and visual field alteration). Bonferroni correction to the α level was applied when tests with multiple comparisons were performed. Unadjusted and multivariate Cox regression were used to assess the effect of different qualitative variables (sex, age, maximal tumor diameter, suprasellar extension, cavernous sinus invasion, type of surgery (microscopic or endoscopic), and radiotherapy) on the absence of tumor and on magnetic resonance imaging (MRI) and complete cure at the last clinical visit. Hazard ratios (HR) and their 95% confidence intervals were calculated. Differences were considered significant when $p < 0.05$.

3. Results

3.1. Clinical features

A group of 131 patients [66 women (50.4%); mean age 52.6 ± 14.8 years (range, 15–82)] was studied. Most patients ($n = 69$; 52.7%) were diagnosed at the age of 40–60 years. Only 3% ($n = 4$) of patients had an age lower than or equal to 25 years diagnosis while in 25.9% ($n = 34$) age at diagnosis was greater than or equal to 65 years. No significant differences in the distribution of patients according to sex and age at diagnosis were found (Fig. 1).

In most patients ($n = 103$; 78.6%) the tumor was symptomatic, while the rest was an incidental finding in imaging study. The main complaint at initial visit was headache ($n = 37$) that appeared in nearly a third of patients (28.2%), followed by alterations in the visual field in 17 patients (13%), mainly as bitemporal hemianopsia, and decreased visual acuity in 12 patients (9.1%). Only 2 patients (1.5%) were diagnosed after a pituitary apoplexy. After the first clinical evaluation, neuro-ophthalmological symptoms were more frequent than endocrine ones (67.2% vs. 31.3%); being visual disturbances and, among them, visual field defects, the main symptoms (55.7%). Erectile dysfunction, decreased libido (6.9%), and asthenia (6.9%) in men (8.4%), and menstrual disorders (6.8%) in women, were the most frequent endocrine symptoms.

3.2. Hormonal study

Pituitary hormonal function was registered in 104 patients (79.4%). Of these, 8 patients (7.7%) had a complete anterior hypopituitarism,

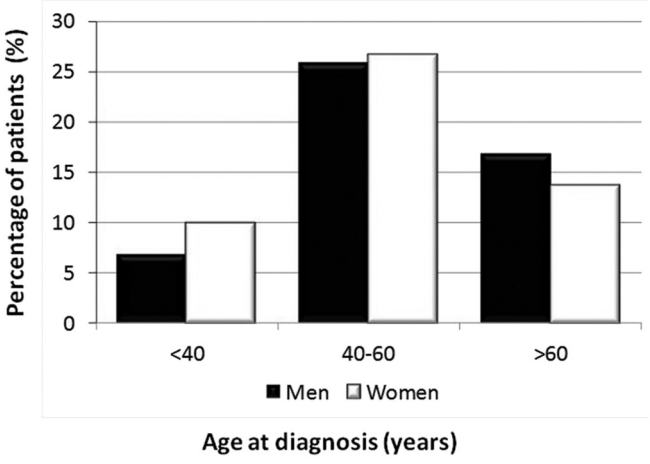

Fig. 1. Percent distribution of 131 patients with NFPA who underwent surgery according to sex and age at diagnosis.

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