The natural course of non-functioning pituitary macroadenomas

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Abstract

Objective: The natural history of non-functioning pituitary macroadenomas (NFMA) has not been completely elucidated. Therefore, we evaluated pituitary function, visual fields, and tumor size during long-term follow-up of non-operated patients with NFMA.

Design: Follow-up study.

Patients: Twenty-eight patients (age 55±3 years) with NFMA, not operated after initial diagnosis, were included.

Results: Initial presentation was pituitary insufficiency in 44%, visual field defects in 14%, apoplexy in 14%, and chronic headache in 7% of the patients. The duration of follow-up was 85±13 months. Radiological evidence of tumor growth was observed in 14 out of 28 patients (50%) after duration of follow-up of 118±24 months. Six patients (21%) were operated, because tumor growth was accompanied by visual field defects. Visual impairments improved in all the cases after transsphenoidal surgery. Spontaneous reduction in tumor volume was observed in eight patients (29%). No independent predictors for increase or decrease in tumor volume could be found by regression analysis.

Conclusion: Observation alone is a safe alternative for transsphenoidal surgery in selected NFMA patients, without the risk of irreversibly compromising visual function.

Introduction

Non-functioning pituitary macroadenomas (NFMA) are the most prevalent pituitary macroadenomas (1, 2). Although NFMA are benign in origin, mass effects may lead to serious clinical symptoms such as visual impairments, chronic headache, and pituitary insufficiency. At the time of initial diagnosis, visual field defects are detected in 60–80% of NFMA patients (3–5). Transsphenoidal surgery is the treatment of choice in NFMA patients with visual field defects. The main aim of surgical treatment is improvement of visual function, which is achieved in over 80% of cases (3, 6). However, most endocrinologists and neurosurgeons probably agree that local tumor control is also an indication for surgery. Macroadenomas elevating the chiasm would be considered an indication for surgery in many centers, even if there are no visual field defects.

Studies on the effect of surgery in NFMA on pituitary function show conflicting results. Some studies report, to a variable degree, an improvement in pituitary function (4, 7–11), whereas others could not demonstrate significant improvement in pituitary function, or even showed decreased pituitary function after transsphenoidal surgery (5, 12, 13). Transsphenoidal surgery leads to long-term tumor control in approximately 80% of patients (3, 14–16), and, in selected series, in even more than 90% of the patients (15, 17).

The natural course of NFMA is largely unknown, because the majority of patients with NFMA are operated. The natural course of pituitary incidentalomas was reported in five previous reports (1, 18–21). In four of these reports, data on the natural course of NFMA were reported (1, 18, 19, 21). The fifth study described the combined data of both non-functioning microadenomas and macroadenomas, not permitting a conclusion with respect to the natural course of NFMA per se (20). Those studies, with a follow-up period ranging from 22 to 73 months, show an increase in the tumor size ranging from 25 to 50% of all patients with NFMA. The natural course of NFMA presenting for other reasons than the presence of an incidentaloma is unclear.

The main indication for surgery in patients with NFMA in our hospital is the presence of visual impairment. In the absence of visual field defects, the initial therapeutic approach is to evaluate tumor growth and visual function with regular intervals. In selected patients with only minimal visual field defects and no evident compression of the optic chiasm, surgery is deferred. The aim of the present study was to evaluate...
changes in pituitary function, visual function, and tumor size during long-term follow-up of these non-operated patients with NFMA.

Patients and methods

Between 1981 and 2005, 232 consecutive patients were diagnosed with NFMA at the Leiden University Medical Center. Patients were included in this study based on the following criteria:

1. Macroadenoma on magnetic resonance imaging (MRI).
3. A prolactin level below 100 μg/l to exclude possible prolactinomas (22, 23).
4. Expectative approach after initial diagnosis.
5. At least two sequential MRI’s to evaluate tumor-growth.

The vast majority of the patients (n=195) was operated after diagnosis. In 37 patients, initially an expectative approach was undertaken after diagnosis. Nine of these patients were not eligible for the present study for the following reasons: follow-up by computed tomography (CT) scan only (n=5), lost to follow-up (n=1), no follow-up by MRI because of very high age and the absence of visual field defects (n=2), and follow-up period shorter than 1 year (n=1). Consequently, a total of 28 patients were included in this study. The duration of follow-up was defined as the interval between the first and the last MRI scan. Since the study was designed to assess the natural course of NFMA, in case of an operation for NFMA, the last MRI before surgery was assigned as the end of follow-up.

An experienced endocrinologist saw each patient at least twice a year. Growth hormone (GH) deficiency was defined as an insulin-like growth factor-I (IGF-I) level below the reference range for age and sex (24), and/or an insufficient rise in GH levels (absolute value <3 μg/l) after stimulation during an insulin tolerance test (ITT). Before 1992, serum GH was measured by RIA (Biolab/serono, Coinsins, Switzerland). The RIA was calibrated against WHO-IRP 66/21, with an interassay variation coefficient below 5%. From 1993 onwards GH was measured by immunofluorometric assay (Wallac, Turku, Finland), calibrated against WHO-IRP 80-505, with an interassay variation coefficient of 1.6–8.4% between 0.1 and 15 μg/l. IGF-I determination was performed by RIA available since 1985 (INCSTAR Corp., Stillwater, MN, USA) with an interassay variation less than 11%. Adrenocorticotropic hormone (ACTH) deficiency was defined as a basal cortisol level at 0800 h of <0.12 μmol/l and/or an insufficient increase in cortisol levels (absolute value <0.50 μmol/l) after an ITT (nadir glucose <2.2 nmol/l). In two patients, an ITT was contraindicated and a corticotropin-releasing hormone (CRH) stimulation test was performed, using human CRH, in which we used the same cut-off levels for cortisol concentrations like in the ITT. During the follow-up, in patients with tumor growth, ACTH-deficiency was tested by basal morning cortisol and an ITT if the morning cortisol was between 0.12 and 0.50 μmol/l. Cortisol was measured with three different immunoassays over time. Until 1986, cortisol was measured by in-house RIA with an interassay coefficient of variation of 10%. Between 1986 and 1994, a fluorescence energy-transfer immunoassay Syva Advance (Syva Company, Palo Alto, CA, USA) was used with an interassay variation coefficient of 3.6–6.1%. From 1994, cortisol was measured by fluorescence polarization assay on a TDx (Abbott). The interassay variation coefficient is 5–6% above 0.5 μmol/l and amounts to 12% under 0.20 μmol/l. In addition, the biannual evaluation consisted of measurement of free T4, luteinizing hormone (LH)/follicle-stimulating hormone (FSH) (all patients), estradiol (premenopausal female patients), and testosterone (male patients) concentrations. Prolactin was measured with a sensitive time-resolved fluoro-immunoassay (Wallac) calibrated against WHO 3rd International Standard for Prolactin 84/500. The interassay coefficient of variation was 3.4–6.2% in the assay range from 3.0 to 80 μg/l.

The evaluation of visual function was done by an ophthalmologist, and included visual acuity, pupillary fundus, and visual fields. Visual fields were assessed by Humphrey perimetry in all patients. Goldman perimetry was used as an additional tool to assess peripheral visual field defects. Ophthalmologic assessment was performed at baseline, after 6 months and subsequently at yearly intervals. Visual field defects were classified as minimal, if there was a small defect in only one eye in only one quadrant.

Repeat MRI was performed within 1 year after the initial diagnosis. If no growth was observed, subsequent MRI scanning was performed every second year. Pituitary apoplexy was defined as radiological evidence of bleeding or infarction in a pre-existent pituitary tumor.

The follow-up of the patients was part of regular medical care. The approaches described in this paper did not involve any randomization or any experimental intervention. According to Dutch law, each patient has to be fully informed on the pros and cons of each treatment strategy, and each patient can only be treated after giving oral informed consent.

Assessment of radiological imaging

Two observers evaluated all MRI scans, independently of each other. Tumor volume was assessed by measuring the largest diameter of the tumor in three directions. The vertical diameter (V) was measured on sagittal T1 weighted and coronal T1 weighted scans,
anteroposterior (AP) diameter on coronal T1 weighted scans and transversal diameter (T) on T1 weighed sagittal scans.

Imaging was performed on MR scanners with different field strengths, ranging from 0.5 to 1.5 T. Imaging parameters included the following: a field of view of 190 mm² and a matrix size of 256×512 mm², yielding an in-plane spatial resolution of 0.74×0.37 mm (scan duration was increased at lower field strengths in order to maintain sufficient resolution). Tumor volume assessment was not performed by the same MRI scanner in each patient, because the higher strength MRIs was not available during the initial part of the observation period of the present study.

Tumor growth was defined as an increase in tumor size on MRI of more than 1 mm (i.e. 2 or more millimeters) in any direction independent of the development of visual field defects.

Tumor volume was assessed as the volume of a rotating ellipsoid with the following formula: \( \pi/6 \times (V \times AP \times T) \) (25).

**Statistics**

Binary logistic regression was performed to assess predictors for increase or decrease in tumor growth. All data are expressed as mean ± standard error unless otherwise mentioned. A \( P \) value of <0.05 was considered statistically significant.

**Results**

**Patient characteristics**

Twenty-eight patients were included. Mean age at presentation was 55 ± 3.3 years. The duration of follow-up was 85 months ± 13 months. Initial presentations were pituitary insufficiency in 44%, visual field defects in 14%, apoplexy in 14%, and chronic headache in 7% of the patients. In only six patients (21%), the macroadenoma was an incidental finding. Radiological imaging revealed a macroadenoma in all cases, with suprasellar extension in 61% and/or lateral/infrasellar extension in 44% of cases. A large number of patients had pituitary insufficiency (71%) of one (32%) or more axes (39%) (Table 1).

Visual field defects were present in 13 patients at initial presentation. In six of these patients the defects were classified as minimal. Visual acuity was normal in six out of seven patients with more than minimal visual field defects.

**Treatment strategy**

Fifteen of the twenty-eight patients were not operated because they had only minimal visual field defects and an intact visual acuity. In these six patients, the MRI revealed a pituitary tumor close to the chiasm, however, without evidence of compression. Four of these patients were relative young and had intact pituitary function. Seven patients were not operated despite visual field defects for the following reasons. The pattern of the visual field defects was not compatible with the diagnosis of chiasm compression and there was a more likely ophthalmologic explanation of the defects (\( N = 2 \)). In two other patients, both with compression of the optic chiasm on MRI, one of which had decreased visual acuity, surgical treatment was contraindicated because of high age and serious co-morbidity. Finally, in three patients with visual field defects and pituitary apoplexy, an initial expectative approach was chosen. In all subjects, a wait-and-see approach was chosen with careful follow-up of the visual function. The three patients with apoplexy were admitted to the ward of endocrinology with close and daily follow-up of visual and endocrine function.

**Radiological follow-up**

All 28 patients had at least two MRI scans, with a mean interval between the first and the last MRI of 85 ± 13 months. Radiological evidence of tumor growth was observed in 14 out of 28 patients (50%) after a duration of follow-up of 118 ± 24 months (see Table 2). In these patients, the mean tumor volume increased from 3489 ± 538 to 5321 ± 820 mm³. The mean increase in tumor size, estimated by the growth in the diameter with the largest growth, was 0.6 mm/year. Growth velocity, expressed in cubic millimeters, was 236 mm³/year. If we exclude the four patients with apoplexy at initial presentation, because in these cases subsequent tumor enlargement is less probable, an increase in tumor volume was observed in 58% of the remaining patients during prolonged follow-up.

Remarkably, reduction in tumor volume was observed in eight patients (29%). Two of those eight patients initially presented with pituitary apoplexy. In the remaining 6 (mean tumor volume 5286 ± 3061 mm³), no change in tumor volume could be detected by MRI. In one patient, despite a follow-up period of 216 months, no tumor growth could be observed.

Binary logistic regression was performed in a model including increase and decrease in tumor volume as dependent variable and age, gender, tumor volume, tumor extension, hypopituitarism, prolactin levels, and follow-up duration as independent variables. No independent predictors for increase or decrease in tumor volume could be found by regression analysis.

**Ophthalmologic follow-up**

In nine of the fourteen patients, tumor growth on MRI was associated with increased defects of visual fields.
MRI characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male/Female</th>
<th>Mean IGF-I SDS</th>
<th>Mean prolactin in male (μg/l)</th>
<th>Mean prolactin in female (μg/l)</th>
<th>Mean IGF-I SDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor volume (mm³)</td>
<td>3746 ± 727</td>
<td></td>
<td>14, range 0.3–50.5</td>
<td>21, range 3.2–42.5</td>
<td>-0.82, range</td>
</tr>
<tr>
<td>Suprasellar extension</td>
<td>61%</td>
<td></td>
<td></td>
<td></td>
<td>-0.20 to 1.17</td>
</tr>
<tr>
<td>Lateral/infrasellar extension</td>
<td>44%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual field evaluation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No visual field defects</td>
<td>54%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal visual field defects</td>
<td>21%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bitemporal visual field defects</td>
<td>25%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Endocrine follow-up

In three of the fourteen patients with growing tumors on MRI, an increase in pituitary deficiencies was observed, whereas in the other eleven patients pituitary functions remained stable. In only one of the eight patients with a decrease in tumor size there was an improvement of pituitary function.

In one of the four patients with pituitary apoplexy, initial pituitary deficiencies were present in three of four axes, including ACTH deficiency. In this patient, pituitary deficiencies resolved within 3 months. The other three patients presented with apoplexy had normal pituitary function.

Six patients were operated because of growth of the pituitary adenoma. In five of these patients, pituitary function remained stable (Table 3). One patient developed both corticotropic and thyreotropic insufficiency after surgery, whereas GH and LH/FSH deficiency persisted.

Long-term outcome

The mean follow-up period was 85 ± 13 months. At the end of follow-up, in 14 patients without signs of tumor growth on MRI, there was still no indication for surgery. Six patients were operated because tumor growth was accompanied by visual field defects. After transphenoidal surgery, visual field defects improved in these six patients. In five other patients with tumor growth, the conservative approach was continued because of normal visual fields (n = 4), or, stable, minimal visual field defects in a high-age female patient (n = 1). Three patients with tumor growth and visual field defects were not operated because of non-compatibility of the defects with compression of the optic chiasm by NFMA (n = 2), or, high age and associated co-morbidity (n = 1). In the last patient, visual field defects were accompanied by a slight decrease in visual acuity (Fig. 1).
In this study, we evaluated the natural course of NFMA. In 28 NFMA patients, with a mean follow-up period of more than 7 years, tumor growth was observed in 14 patients (50%). In seven of these patients, tumor growth was accompanied by (increased) visual field defects, likely to be caused by mass effects of the tumor. Surgical intervention was performed in only 21% (n = 6) of all patients and improved visual fields in all cases. Remarkably, a spontaneous decrease in tumor volume was observed in 29% of the patients during long-term follow-up. Therefore, in the absence of visual impairments, observation alone is a safe alternative for surgery in selected patients with NFMA, especially in patients without compromised pituitary function and without compression of the optic chiasm.

To date, only four studies reported the natural course of NFMA, discovered as incidentalomas, comprising a total of 41 patients (1, 18, 19, 21), whereas an additional study reported the natural course of a combined series of both non-functioning micro- and macroadenomas (20). Those studies, summarized in Table 4, with a follow-up period of 22–73 months, report an increase in tumor size in about 25–50% of the patients. However, several aspects of the design of the present study were different from those previous studies. We included all NFMA patients, in whom surgery was not performed for any reason. In contrast to these previous studies, an incidentaloma was the initial finding in only a minority of our patients. Therefore, the characteristics of our study population are different, with a higher prevalence of pituitary insufficiency and visual field defects than those in the previous studies (1, 19).

Previous studies also showed that tumor growth does not invariably lead to visual field defects (1, 18, 20, 21). In our series, tumor growth (n = 14) was accompanied by visual field defects in only nine patients. Moreover, in only seven of these patients, the pattern was compatible with tumor mass effect. In all patients operated for tumor growth and visual field defects, these defects improved or normalized. These data suggest that in case of the development of visual field defects in the course of NFMA, surgical outcome still is favorable with respect to visual field defects. These results are in accordance with the observations in surgical series which documented...
improvement of visual field defects in 80% of NFMA patients after transsphenoidal surgery (3, 6).

In pituitary microadenomas in general, tumor growth is observed in only a minority of the patients, in contrast to NFMA. Moreover, in microadenomas, the chance of tumor growth seems to be almost outweighed by the change of a decrease in tumor size (1, 20). In patients with NFMA, the tumor already has demonstrated a propensity for growth. Nonetheless, after a mean follow-up period of 85 months, no tumor growth could be detected in this study in 50% of cases. However, at initial presentation, the rate of tumor growth cannot be predicted in individual patients. In our study, no independent predictors for increase or decrease in tumor volume could be found by binary logistic regression. In six patients, in the absence of radiological signs of pituitary apoplexy, a decrease in tumor volume was observed. We speculate that this unexpected phenomenon is caused by clinically silent and radiological undetectable ischemia of the tumor.

In patients with NFMA, it is a reasonable approach to repeat MRI 1 year after initial diagnosis, in order to make a first estimation of tumor growth. In our study, in patients with tumor growth, the mean increase in diameter was only 0.6 mm/year, which is below the detection limit of MRI. These data suggest that, for further follow-up, an approach with a repeat MRI every second year is safe and optimal for the detection of possible tumor growth. However, this recommendation is a generalization and exact timing for re-evaluation of tumor growth and repeat MRI has to be determined in an individualized way, depending on symptoms, size of tumor elevation, etc.

Table 4 The natural course of tumor volume in non-functioning pituitary macroadenomas.

<table>
<thead>
<tr>
<th>Author</th>
<th>Macroadenoma</th>
<th>Mean follow-up</th>
<th>Increase in tumor volume</th>
<th>Decrease in tumor volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feldkamp et al. (1)</td>
<td>N=19</td>
<td>32 Months</td>
<td>N=5</td>
<td>N=1</td>
</tr>
<tr>
<td>Donovan et al. (18)</td>
<td>N=16</td>
<td>73 Months</td>
<td>N=4</td>
<td>N=0</td>
</tr>
<tr>
<td>Reincke et al. (19)</td>
<td>N=7</td>
<td>22 Months</td>
<td>N=2</td>
<td>N=0</td>
</tr>
<tr>
<td>Sanno et al. (20)</td>
<td>N=115a</td>
<td>51 Months</td>
<td>N=23</td>
<td>N=11</td>
</tr>
<tr>
<td>Arita et al. (21)</td>
<td>N=42</td>
<td>62 Months</td>
<td>N=21</td>
<td>N=1</td>
</tr>
<tr>
<td>Present series</td>
<td>N=28</td>
<td>85 Months</td>
<td>N=14</td>
<td>N=8</td>
</tr>
</tbody>
</table>

*aConsisting of both non-functioning pituitary microadenomas and macroadenomas.

The possibility of pituitary apoplexy must be taken into account in the discussion of surgical versus conservative management of non-functioning macroadenomas. Apoplexy is a clinical syndrome resulting from acute hemorrhage or infarction of the pituitary tumor (33). In unselected patients with NFMA, apoplexy is the presenting sign in 15–25% of the patients (12, 34). Only a minority of patients presenting with apoplexy were known to harbor a pituitary tumor (35). In contrast, the incidence of apoplexy in patients already known to have a pituitary tumor is estimated to be less than 1% per year (20). In patients with macroadenomas, the incidence of apoplexy is probably higher (21). The occurrence of pituitary apoplexy has been described following pituitary function tests (36), coronary artery bypass surgery (35, 37), cholecystectomy (38), head trauma (39), and...
vaginal delivery (40). Moreover, apoplexy has been associated with hypertension (35) and anticoagulant therapy (40). The majority of patients with pituitary apoplexy present with ACTH-deficiency (35), establishing the potential life-threatening condition of the clinical syndrome. In the present series four patients presented with pituitary apoplexy. In three of these cases, apoplexy was accompanied by visual field defects, and one patient had multiple pituitary deficiencies. During follow-up, both the visual field defects as well as the pituitary deficiencies resolved within 3 months. Although the optimal treatment for NFMA patients presenting with pituitary apoplexy is still a matter of debate (41–43), surgical intervention is indicated in patients presenting with total or near-total visual loss. After transsphenoidal surgery, visual impairment and ocular paresis resolves in the majority of cases (41–43). There are no randomized controlled trials on surgical versus conservative treatment of pituitary apoplexia. Nonetheless, patients with classical pituitary apoplexy, who are without neuro-ophthalmic signs or exhibit mild and non-progressive signs, can be managed conservatively in the acute stage (35). In our hospital, we favor a conservative approach, unless visual acuity is impaired. In another series, we have included eight patients with apoplexia who were operated for that reason (12). Our study confirms that in three patients that conservative management with careful follow-up is appropriate in selected patients without, or with only mild neuro-ophthalmic signs, without adversely affecting patient outcomes.

In conclusion, our series with non-operated NFMA patients report an increase in tumor size in 50% of all patients during long-term follow-up, accompanied by visual field defects in 50% of these cases. In patients with an increase in tumor size and visual field defects, surgical treatment resolved the visual field defects. No independent predictors for tumor growth were found by logistic regression. Based on these data, we propose a conservative approach in selected patients with NFMA without visual field defects. In these patients, this is a safe alternative for transsphenoidal surgery, without the risk of irreversibly compromising visual field defects.

References


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