Nonfunctioning pituitary macroadenomas : treatment and long-term follow-up

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Progressive improvement of impaired visual acuity during the first year after transsphenoidal surgery for nonfunctioning pituitary macroadenoma

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CHAPTER 4

SUMMARY

Objective. Improvement of visual field defects continues even yr after the initial surgical treatment. Because this process of continuing improvement has not been documented for visual acuity, we audited our data to explore the pattern of recovery of visual acuity until one year after transsphenoidal surgery for nonfunctioning pituitary macroadenoma.

Design. Retrospective follow-up study

Patients. Forty-four patients (mean age 56 ± 14 yr), treated by transsphenoidal surgery for nonfunctioning pituitary macroadenoma, were included in this analysis.

Results. Visual acuity improved significantly within three months after transsphenoidal surgery. The mean visual acuity increased from 0.65 ± 0.37 to 0.76 ± 0.36 ($p<0.01$) (right eye), and from 0.60 ± 0.32 to 0.82 ± 0.30 ($p<0.01$) (left eye). Visual acuity was improved one year after transsphenoidal surgery compared to the three months postoperative values. The mean visual acuity increased from 0.76 ± 0.36 to 0.82 ± 0.34 ($p<0.05$) (right eye), and from 0.82 ± 0.30 to 0.89 ± 0.27 ($p<0.05$) (left eye).

Conclusion. Visual acuity improves progressively after surgical treatment for nonfunctioning pituitary macroadenomas, at least within the first year after transsphenoidal surgery.

INTRODUCTION

Nonfunctioning pituitary macro-adenomas (NFMA) are the most prevalent macro-adenomas (1;2). Patients with NFMA mainly present with decreased visual acuity, visual field defects and hypopituitarism, caused by mass effects of the tumor (3-5). Transsphenoidal surgery is the treatment of choice, resulting in improvement of visual field defects in 75-100% of all patients (3-5). Accordingly, visual acuity improves in the majority of patients (6-10), although visual field defects and visual acuity may worsen in a limited number of patients after surgery (6;7;9;10).

The process of visual field recovery starts directly after surgery and can already be documented on the second postoperative day (11). This process of recovery is probably due to restoration of the velocity of conduction. However, improvement of visual field defects continues even yr after the initial surgical treatment (12;13). Although a reduced visual acuity is correlated with the extent of visual field defects (13;14), postoperative changes in visual acuity do not parallel changes in visual fields in every case (6).

To our knowledge, the process of gradual visual improvement has only been observed for visual field defects, but not for visual acuity (12). This is, however, clinically relevant since improvement of minor visual field defects can occur unnoticed, whereas improvement in visual acuity is almost invariably noticed, and can potentially overcome thresholds to previous impairments in daily life. We therefore audited our data to explore the pattern of recovery of visual acuity until one year after transsphenoidal surgery for nonfunctioning pituitary macroadenoma.

PATIENTS AND METHODS

Patient selection

Forty-four patients, mean age 56 ± 14 yr, were included in this retrospective analysis. In order to obtain a homogenous cohort for assessment, the inclusion criteria were the following:

1. Transsphenoidal surgery for nonfunctioning pituitary macroadenoma (diameter > 1 cm) for compression of the optic chiasm
2. Assessment of visual acuity at least once before surgery and at least twice in the first year after surgery
3. The availability of two postsurgical MR scans within a time frame of maximal three months of the ophtalmological assessments

To overcome the potential effect of postoperative tumor-regrowth on visual outcome, patients were excluded from analysis if the one-year post-operative scans revealed growth of residual tumor.

For complete assessment, we reviewed the patient records of all departments involved in the treatment of NFMA (Endocrinology, Neurosurgery, Ophthalmology). Endocrine (pituitary function) and ophthalmologic data (visual acuity and visual fields) were assessed before surgery, 3, and 12 months after surgery. An MRI was performed before surgery, 3-6 months, and 12-15 months after surgery. Transsphenoidal surgery was performed by one of two neurosurgeons.

Corrected visual acuity was determined by the Snellen chart (15;16) and was scored for both eyes. Visual fields were assessed by Humphrey perimetry in all patients. Goldman perimetry was used as an additional tool to assess peripheral visual field defects.

Definitions

The diagnosis of nonfunctioning pituitary macroadenoma was based on two criteria: 1) the presence of a pituitary macroadenoma (>1cm) on MRI, 2) the absence of overproduction of any of the pituitary hormones. In all cases the diagnosis was histological confirmed. Tumor extension was classified as suprasellar, parasellar/infrasellar or combined suprasellar and parasellar/infrasellar extension.

In all patients, visual acuity was scored on a scale between 0 and 1.25. Visual field defects were scored semi-quantitative and classified as mild, moderate or severe. Visual field defects were classified as mild, if there were peripheral defects in only one quadrant. Defects were classified as moderate if the upper quadrants were affected, whereas in combined upper and lower quadrant field defects these were classified as severe.

Growth hormone (GH) deficiency was defined as an insufficient rise in GH levels (absolute value < 3 μg/L) after stimulation during an insulin tolerance test (ITT). When secondary amenorrhoea was present for more than 1 year premenopausal women were defined as LH/FSH deficient. Postmenopausal women were defined as LH/FSH deficient when gonadotropin levels were below the normal post-menopausal range (LH < 10 U/l, FSH < 30 U/l). In men, LH/FSH deficiency was defined as a testosterone level below the reference range (8.0 nmol/L). TSH deficiency was defined as a total or free T4 level below the reference range. ACTH deficiency was defined as a basal cortisol level at 8.00 A.M. of < 0.12 μmol/l and/or an insufficient increase in cortisol levels (absolute value < 0.55 μmol/ l) after an ITT.

Statistical analysis:

The paired t-test was used for paired samples. SPSS software version 12.0 (SPSS Inc., Chicago, IL, USA) was used. A P-value of < 0.05 was considered statistically significant.

RESULTS

Preoperative patient characteristics (Table 1)

Forty-four patients, 52% male, were included in this study. Radiological imaging by MRI revealed a macro-adenoma in all patients with suprasellar extension in 100% and parasellar/infrasellar extension in 41% of cases. Hypopituitarism was present in 80% of all patients and panhypopituitarism in 25%.

Preoperative assessment of visual function (Table 1)

Visual fields were normal in 9% (5/44) off all patients. Transsphenoidal surgery in these patients was performed for apoplexia (n=1) and because compression of the optic chiasm was evident on the MR scan (n=4). Of all patients with visual field defects 59% were classified as severe, 17% as moderate, and 12% as mild. Mean visual acuity was 0.65 ± 0.37 for the right eye, 0.60 ± 0.32 for the left eye.

Visual acuity was assessed twice before surgery in 34 patients (77% of total). The median time between the first and the second pre-surgical assessment was 4 weeks (range 1-45). No significant decrease in visual acuity was observed within this time period. The mean visual acuity for the two pre-surgical assessments was: 0.65 ± 0.37 vs 0.66 ± 0.38 (right eye), and 0.60 ± 0.32 vs 0.62 ± 0.33 (left eye). Moreover, no decrease in visual acuity was observed in patients (n=13) with a time interval of > 8 weeks between the first and the second pre-surgical assessment.

Table 1. Patient characteristics before transsphenoidal surgery

Male/female	23/21
Age (yr ± SD)	56 ± 14
Visual acuity	
Oculus dexter (mean ± SD)	0.67 ± 0.37
Oculus sinister (mean ± SD)	0.61 ± 0.33
Visual field defects	
Severe	59%
Moderate	17%
Mild	12%
None	12%
Pituitary function	
GH deficiency	77%
LH/FSH deficiency	71%
ACTH deficiency	45%
TSH deficiency	38%
Panhypopituitarism	25%
MRI characteristics	
Suprasellar extension	100%
Infrasellar/parasellar extension	41%

Surgical treatment

All patients were treated by transsphenoidal surgery. Repeat surgery within 6 months after initial treatment was performed twice (large residual tumor mass (n=1) and persisting liquor leakage (n=1)). Repeat surgery was performed by transcranial approach.

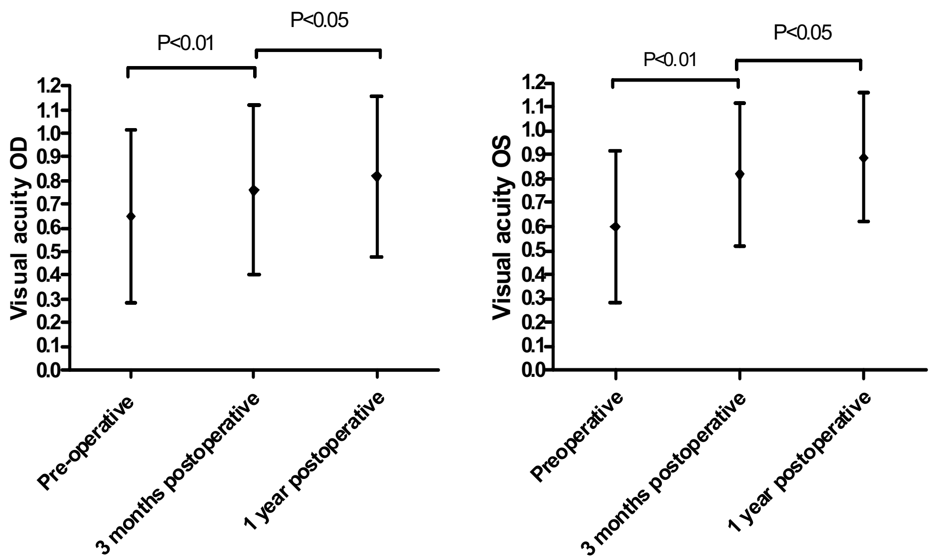
Transsphenoidal surgery was followed by radiotherapy in 10 patients in order to prevent recurrence. Patients received 40 Gy (n=5) or 46 Gy (n=5).

Three months postoperative assessment of visual function

After transsphenoidal operation in patients with preoperative visual field defects improvement was observed in 60% and normalisation of the visual fields in 32%. In 1 patient there was a slight increase in visual field defects.

Visual acuity improved significantly three months after transsphenoidal surgery (Figure 1). The mean visual acuity increased from 0.65 ± 0.37 to 0.76 ± 0.36 (p<0.01) (right eye), and from 0.60 ± 0.32 to 0.82 ± 0.30 (p<0.01) (left eye).

Figure 1. The pattern of improvement of visual acuity after transsphenoidal surgery for nonfunctioning pituitary macroadenomas (n=44)



One-year postoperative assessment of visual function

One year after initial surgical therapy visual field defects showed continuous improvement in 35% patients, compared with early postoperative results. In 80% of these patients, this improvement was accompanied by continuous improvement of visual acuity.

In 55% of all patients (n=24), visual acuity shows continuing improvement until one year after surgery. In 8 of them, this improvement was not accompanied by further improvement of visual field defects. Visual acuity was improved one year after transsphenoidal surgery compared with the three months postoperative values (Figure 1). The mean visual acuity increased from 0.76 ± 0.36 to 0.82 ± 0.34 ($p<0.05$) (right eye), and from 0.82 ± 0.30 to 0.89 ± 0.27 ($p<0.05$) (left eye).

DISCUSSION

The main aims of surgery in nonfunctioning pituitary macroadenomas are restoration of visual acuity and visual field defects by decompression of the optic chiasm. Nonetheless, our data indicate that there is no necessity for immediate decompression since postponement of surgery for several weeks did not result in deterioration of visual acuity. Moreover, in this series of 44 patients, we demonstrated a continuing improvement of visual acuity until one year after transsphenoidal surgery.

There is a significant correlation between the severity of visual loss prior to surgery and persisting visual field defects (9;13;14). In our patients in whom visual acuity was assessed twice before surgery, no decrease of visual acuity was observed with a median time interval between two measurements of 4 weeks. This indicates that postponing surgery for one month does not negatively influence visual outcome, which is in line with the slow growth pattern of nonfunctioning adenomas (4). Nonetheless, the delay of surgery should not unnecessarily be prolonged because a significant, inverse, correlation between visual outcome and the prolonged duration of symptoms has been reported (9).

The initial event in the pathogenesis of decreased visual function in pituitary macroadenomas is compression of the optic chiasm. Nerve compression leads to decreased conduction and demyelination. In an experimental setting, the process of demyelination after nerve compression has been observed even after two days (17;18). In case of continuous nerve compression remyelination can be observed after several weeks, although remyelinated fibres do not seem to reach normal thickness and organisation structure, and complete demyelinated fibres co-exist (17;18). Re-myelinated fibers restore conduction, at least partially, even if the causative nerve lesion is still existing (19;20). The improvement of visual dysfunction after surgical treatment is supposed to consist of two, or probably even three, phases (12). There is an early phase, comprising the first hours and days after surgery. In this early fast phase, the improvement is caused by decompression of the visual pathways, leading to a restoration of signal conduction. Visual recovery has been demonstrated in the first days after surgical treatment (11;12). The second phase, i.e. delayed recovery, is pathophysiologically caused by restoration of axonal transport and remyelination and based on remyelination of the optic nerve vessels. This phase of delayed recovery may last for several yr (12;13). A precise boundary between the end of the fast phase of recovery and the start of the delayed recovery seems to be artificial, because these two phases reflect different pathophysiological mechanisms, which may co-exist for a certain time-period. The contribution of the first phase of recovery might be larger, given the fact that more than 50% of eventual recovery takes place within the first three months after surgery (13).

It is already known that visual acuity improves in the first months after surgical treatment (6-10) and that the improvement of visual field defects is a continuing process for at least one year (12;13). Kerrison *et al.* (12) showed progressive improvement of visual fields even more than two yr after surgical decompression of the optic chiasm. However, they did not demonstrate this same pattern of recovery for visual acuity. This might be due to the relative small number of patients during prolonged follow-up. In the present study we demonstrate that also improvement of visual acuity continued one year after surgical treatment.

The clinical consequences of the delayed phase of recovery for both visual field defects and visual acuity are obvious. Follow-up of patients after surgical treatment for pituitary macroadenomas should include ophthalmologic assessment within several weeks after surgery, as well as subsequent assessments after one and two years, in order to estimate the final effect of surgery on visual function. Moreover, patients should be told that visual function can continue to improve at least until one year after surgery. The relevance of these findings is obvious and is of importance to all patients, given the impact of a decreased visual acuity as an independent predictor for a decreased quality of life (21;22). Moreover, these data are essential in order to evaluate potential effects of recurrent pituitary adenomas on visual function.

Ten patients in our series received postoperative radiotherapy. However, it is unlikely that this treatment affected the results of our study. In a series reported by Gnanalingham *et al.* (13), in which 34% of all patients received postoperative radiotherapy, persistent improvement of visual field defects was documented even yr after surgical therapy. In another series of 21 patients, 2 yr after pituitary irradiation, there were no cases of radiation-induced visual field or visual acuity deterioration (23).

In conclusion, this study demonstrates that the improvement of visual acuity after transsphenoidal treatment for nonfunctioning pituitary macroadenomas consists of both an early and a delayed phase of recovery. After initial post-surgical recovery, a progressive delayed improvement of visual acuity at least until one year after transsphenoidal surgery is likely to occur.

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