Treatment of nonfunctioning pituitary adenomas: What were the contributions of the last 10 years? A critical view

Alberto M. Pereira *, Nienke R. Biermasz

Department of Endocrinology and Metabolism, Leiden University Medical Center, C4-R, PO Box 9600, 2300 RC Leiden, The Netherlands

Abstract

Objectives.– All evidence for treatment and follow-up for nonfunctioning pituitary adenomas (NFMA) is based on observational studies. The objective was to critically review the contributions of the last 10 years on treatment of NFMA.

Materials and methods.– Systematic review.

Results.– Transsphenoidal surgery remains the cornerstone of treatment of NFMA. When compared to the microsurgical procedure, some, but not all, studies favor endoscopy, but endocrinological outcome is not different. Radiosurgery results in a high and durable rate of tumor control, including in those previously treated by conventional radiotherapy, but the risk of developing hypopituitarism is comparable to the risk after conventional radiotherapy. In selected patients without visual field defects, a wait-and-see approach with frequent evaluation of visual fields is possible, without the risk of irreversibly compromising visual function. Tumor progression in NFMA is difficult to predict, but the MIB-1 LI is clinically useful and is indicative of invasiveness, but does not predict recurrence. To date, the potential contribution of other proliferation markers still requires further validation, and effective medical treatment strategies are not available. New features are the role of temozolomide and rapamycin as potential therapeutic targets, combined with octreotide. Although chimeric sst-DA analogues effectively inhibit proliferation in vitro, the effects of these molecules have not yet been evaluated in clinical trials with patients with NFMA.

Conclusion.– Surgery, followed by radiotherapy or radiosurgery in case of remnant or recurrence, remains the cornerstone of treatment of NFMA. Currently, medical treatment cannot yet be incorporated in routine clinical practice.

© 2012 Elsevier Masson SAS. All rights reserved.

Résumé

Objectif.– Toutes les preuves recueillies pour baser le traitement et le suivi des adénomes hypophysaires non fonctionnels proviennent d’études d’observation. L’objectif de cet article est donc de revoir de manière critique la contribution des dix dernières années sur le traitement des adénomes hypophysaires non fonctionnels.

Matériel et méthodes.– Revue systématique. Résultats.– La chirurgie transsphénoidale reste le pilier du traitement des adénomes hypophysaires non fonctionnels. Quand on compare les techniques microchirurgicales, certaines des études, mais pas toutes, sont en faveur de l’endoscopie. Cependant, les résultats, en termes endocrinologique, ne sont pas différents. La radiochirurgie produit un taux élevé et durable de contrôle tumoral, y compris chez les patients préalablement traités par radiothérapie conventionnelle mais le risque de développer une insuffisance hypophysaire est comparable au risque observé après radiothérapie conventionnelle. Chez les patients sélectionnés qui n’ont pas de troubles visuels, une simple surveillance, avec une évaluation fréquente des champs visuels, est possible sans risque de compromettre de manière irréversible la fonction visuelle. La progression tumorale dans les adénomes non fonctionnels est difficile à prédire mais le Ki67 est cliniquement utile : il est indicatif de l’invasion mais ne prédit pas la récidive. Actuellement, la contribution potentielle d’autres marqueurs de prolifération nécessite encore une validation. Des stratégies médicamenteuses efficaces ne sont pas actuellement disponibles. De nouvelles thérapeutiques comme le témozolomide ou la rapamicine pourraient être utiles en combinaison avec l’octréotide dans certains cas. Si les analogues chimériques somatostatine-dopamine inhibent de manière efficace la prolifération in vitro, les effets de ces molécules n’ont pas été évalués dans des essais cliniques chez les patients ayant des adénomes hypophysaires non fonctionnels.

Conclusion.– En conclusion, la chirurgie, suivie de la radiothérapie ou de la radiochirurgie en cas de reliquat ou de récidive reste le pilier du traitement des adénomes non fonctionnels. Actuellement, le traitement médicamenteux ne peut pas être incorporé à la stratégie thérapeutique en pratique clinique de routine.

© 2012 Elsevier Masson SAS. Tous droits réservés.

1. Introduction

Clinically nonfunctioning pituitary adenomas (NFMA) are benign tumors characterized by the absence of clinical and
biochemical evidence of hormonal overproduction. Therefore, signs or symptoms do not occur until the mass effects induce pituitary insufficiency or visual field defects (in case of suprasellar extension) [1].

All evidence for treatment and follow-up for nonfunctioning adenomas is based on observational studies. When optic function is compromised, transsphenoidal surgery is the preferred treatment leading to improvement or even complete restoration of visual field defects in the majority of the cases [1,2]. Reversal of hypopituitarism is uncommon [3]. Radiotherapy is reserved for those cases with incomplete resection and in case of tumor regrowth or recurrence. In selected cases, when visual field defects are absent, and the tumor is not too close to the optic chiasm, a wait-and-see approach is possible, since tumor growth is usually slow albeit unpredictable [1,3]. Medical treatment, with either dopamine agonists or somatostatin analogues, has not been incorporated into routine clinical practice, because the results of historically treated cohorts of nonfunctioning pituitary adenomas have been somewhat disappointing [4,5]. The aim of this systemic literature review was to evaluate the potential contributions of new treatment modalities published in the last decade.

2. Methods

An electronic database search in PubMed was performed on 23 December 2011 for all articles involving nonfunctioning pituitary adenomas and its treatment, from 1st January 2002, onwards, using the following search strategy:

(“nonfunctioning pituitary macroadenoma” OR “nonfunctioning pituitary microadenomas” OR “nonfunctioning pituitary adenoma” OR “nonfunctioning pituitary adenomas” OR “non-functioning pituitary macroadenoma” OR “non-functioning pituitary macroadenomas” OR “non-functioning pituitary adenoma” OR “non-functioning pituitary adenomas” OR “non-functioning pituitary macroadenomas” OR “non-functioning pituitary adenomas” OR “non-functioning pituitary adenomas” OR “non-functioning pituitary adenomas” OR “nonfunctioning pituitary macroadenoma” OR “nonfunctioning pituitary macroadenomas” OR “nonfunctioning pituitary adenoma” OR “nonfunctioning pituitary adenomas” OR (pituitary[ti] AND (adenoma[ti] OR adenomas[ti] OR macroadenoma[ti] OR macroadenomas[ti])) “Pituitary Neoplasms” [majr]) AND (nonfunctioning OR “non-functioning”) AND (treatment OR therapy OR surgery OR radiotherapy OR therapeutic OR surgical OR radiology OR radiosurgery OR radiotherapy OR radiological OR radiotherapy OR monitoring OR management) AND (“2002” [PDAT]; “3000” [PDAT]) NOT (“Case Reports” [Publication Type] OR “Review” [Publication Type]).

The search resulted in 225 articles (329 in the initial search, of which 112 were case reports or reviews). Only original articles in the English, German, and French languages were included. In addition, studies were excluded when the study was restricted to elderly patients (>80 years) or adolescents and children, transcranial surgery, or when cases were selected based on immunohistochemistry only. In case of (partial) duplication of cohorts, the paper with the longest duration of follow-up was included.

Of the remaining 225 articles, 119 were excluded based on title and abstract. The remainder 106 articles included: outcome of microsurgical or endoscopic surgery (n=23), outcome of conventional radiotherapy (n=5) or radiosurgery (n=16), medical treatment (n=1), natural course/wait-and-see approach (n=6), follow-up management strategies: radiological follow-up, scintigraphy during follow-up (n=8), the effects of treatment with rGH on tumor recurrence (n=5), and pituitary tumor expression markers in relation to biological behavior or treatment (n=42). This review highlights on the most important contributions on the treatment efficacy in nonfunctioning pituitary adenoma of new transsphenoidal surgical approaches, on radiosurgery, on a wait-and-see approach, and on studies aimed at the identification of new markers in relation to tumor behavior or response to treatment.

3. The efficacy of new surgical procedures

A total of 23 studies evaluated the efficacy of transsphenoidal surgery, using either the conventional microsurgical approach or the endoscopic approach, including a few studies with advanced methods such as intraoperative optic nerve identification (n=1), intraoperative MRI (n=1), or with pituitary transposition (n=1).

Ten of these studies, including a total of 854 patients, evaluated the endoscopy, which included mainly pre-selected patients with either invasive or recurrent or persistent adenomas [6–9]. Dehdashi et al. evaluated their surgical results performed via the endoscopic approach in a relatively large cohort of 111 patients, and found comparable remission rates after a median follow-up of 19 months as historical cohorts operated via microsurgery [10]. A systematic review on microscopic versus endoscopic pituitary surgery (not restricted to NFMA!) that included 11 studies published between 1989 and June 2009 did not find any differences in gross total tumor resection or endocrinological outcome [11]. However, the endoscopic approach reduced operating time, hospital stay, perioperative morbidity (lumbar drains, postoperative diabetes insipidus, and rhinologic complications) and hospital stay, as well as patient discomfort. Importantly, visual outcome was not incorporated in the outcome measures. Two recent series, however [12,13], directly compared endoscopy versus microsurgery within their own center and found an increase in the quality of adenoma removal (as reflected by gross total removal [74% vs 50%] with greater control of lateral and suprasellar extension) after endoscopy with similar morbidity 1 year after surgery. In addition, endoscopy improved endocrinological outcome, as reflected by anterior pituitary function after surgery (improvement 56% vs 25%, stabilization 22% vs 46%, and aggravation 22% vs 29%; P=0.01). Improvement in visual field defects was comparable (100% vs 93%). Thus, in contrast to the results of the systematic review [11] that included all pituitary adenomas treated between 1989–2009, these new data indicate that gross total tumor resection rate is consistently higher for endoscopy compared with microscopy, in the presence of comparable effects on visual outcome and favorable effects on pituitary function, in some, but not all studies.

Recently, Taussky and colleagues reported on the long-term results of a new surgical technique: pituitary transposition, or hypophysopexy [14]. This technique aims to reduce the radiation dose to the normal pituitary in cases of planned radiotherapy of residual tumor within the cavernous sinus. The technique of pituitary transposition involves placement of a fat graft between

the normal pituitary gland and residual tumor in the cavernous sinus. After sellar exploration, the pituitary gland is transposed from the region of the cavernous sinus, and the graft is interposed between the pituitary gland and the residual tumor. The residual tumor may then be treated with conformal fractionated radiation therapy or stereotactic radiosurgery. After hypophysopexy, none of the 34 patients (of which 19 patients with nonfunctioning pituitary adenomas) developed new hypopituitarism after a median follow-up of 4 years after radiosurgery or fractionated stereotactic radiotherapy. This implies that in selected cases of residual tumor invading the cavernous sinus, pituitary transposition may reduce the incidence of radiation induced pituitary insufficiency.

4. The efficacy of radiosurgery

Since 2002, a total of 15 studies involving approximately 600 patients with NFMA have evaluated the treatment efficacy of radiosurgery. All studies were retrospective evaluations, with a median follow-up duration of ranging from 21–80 months, and with a median dose to the tumor margin between 16–25 Gy. The tumor control rate, defined as stabilization or a decrease in tumor volume, varied from 67–97% in previously irradiated tumors [15–17], but was as high as 95–100% in radiation naive patients even after 7 years [15–25]. Late toxicity of cranial neuropathy was rare and reported in five patients only (less than 1% of total) [18,21,24]. The development of new pituitary deficiencies, however, was documented in 8–10% of the patients after 2–3 years and 32–42% after 5 years [17,19,20,22,25]. These data indicate that radiosurgery results in a high and durable rate of tumor control in patients with a nonfunctioning pituitary adenoma, including in those previously treated by conventional radiotherapy. The primary complication is hypopituitarism, and the risk of developing new anterior pituitary deficits appears to correlate with the size of the irradiated tumor [22].

5. Observing the natural course in a wait-and-see approach

There is an increasing awareness that in selected cases, a wait-and-see approach is possible, at least at the time of diagnosis, and surgery is not always required. To date, the efficacy of such an approach has been retrospectively evaluated in three reports that included a total of 74 patients. The first study [26] involved 28 non-operated NFMA patients after a mean follow-up of 118 months and found an increase in tumor size in 50% of patients, accompanied by visual field defects in 50% of these cases. In patients with an increase in tumor size and visual field defects, surgical optic decompression resolved the visual visual field defects in all cases. No independent predictors for tumor growth were found by logistic regression. The second study [27] evaluated 40 patients with nonfunctioning adenomas during a mean follow-up duration of 42 months. Importantly, 16 of these harbored microadenomas, and in contrast to the study reported by Dekkers et al. [26], patients with apoplexy were not included. In agreement with Dekkers et al., they found a 50% increase in size in macroadenomas, but also in 12.5% of microadenomas. However, new or deterioration of visual field defects was only observed in the macroadenomas. The visual outcome of the patients that subsequently underwent surgical decompression was not reported. The third study [28] reported on the natural course of NFMA in only six patients, all with radiological evidence of compression of the optic chiasm although only one patient had visual field defects at baseline. During a mean follow-up of 41 months, two of the six patients developed visual field defects, while the single patient with visual field defects at baseline improved to normal vision. These observations indicate that in selected patients with NFMA without visual field defects, a conservative approach can be proposed. In these patients, this seems to be a safe alternative for transsphenoidal surgery, without the risk of irreversibly compromising visual field defects. However, more data on the natural course are urgently needed before definite advice can be incorporated in clinical guidelines.

6. The identification of new markers in relation to tumor behavior or response to treatment

We have recently demonstrated that recurrence rate differs between pituitary adenomas, being highest in patients with prolactinoma. Patients with NFMA have a lower chance of remission than patients with functioning adenomas. The post-operative basal hormone level is the most important predictor for recurrence in functioning adenomas, but in NFA no specific factor predicted recurrence [29].

A number of 42 studies evaluated the expression of various markers in nonfunctioning adenoma tissues in relation to tumor behavior or response to treatment. These markers of interest were first of all classical markers of cell proliferation: p53, Ki67, or MIB-1 labeling indices, but also many potentially new markers for invasiveness, like DNA topoisomerase I (Topo I), O(6)-methylguanine DNA methyltransferase (MGMT), PPARgamma receptors, survivin, angiogenic factors like VEGF and FIK-1 (fetal liver kinase 1), MMP-2, MMP-9, and PKC-alpha or PKC-delta, Interleukin 4 receptor (IL-4R) complex, but also Raf/MEK/ERK and PI3K/Akt/mTOR pathways and very recently Notch3 mRNA and protein over expression. In addition, other studies evaluated the expression of somatostatin receptor and dopamine receptor subtypes with the subsequent in vitro responses to various chimeric molecules that bind both specific somatostatin and dopamine receptor subtypes. Not every individual paper is discussed.

MIB-1 expression and or its labeling indices in relation to clinical behavior of NFMA were evaluated in five studies. The first study found no difference in the p53 or MIB-1 labeling indices between recurrent and non-recurrent NFMAAs [30], but Tanaka et al. [31] investigated the relation between MIB-1 index and the tumor volume doubling time (TVDT) in 40 patients and found an inverse correlation between the log TVDT and MIB-1 index ($r = -0.49$), and between the MIB-1 index and patient age ($r = -0.61$). The difference between the TVDT noted in the patients younger or older than 61 years was highly significant (1106 days vs 2566 days). This was also reflected in the age (50.8 ± 15.3 years) of the patients with rapidly growing tumors (TVDT < 1836 days, 24 patients) and the age (69.1 ± 7.6 years)
of the patients with slowly growing tumors (TVDT > 1836 days, 14 patients). Thus, the tumor growth rate of residual NFMAs is strongly influenced by age, being much longer in elderly patients. In agreement, another two studies also found that the MIB-1 LI was significantly correlated with the MRI detected tumor volume doubling time of postoperative residual adenomas [32,33]. However, no relation between MIB-1 LI and the rate of recurrence was found in a relatively large cohort of 85 patients [34]. Finally, no differences between the expressions of Ki-67, p53, and also AIP were found in invasive versus noninvasive nonfunctioning adenomas in a recent study in 29 cases [35]. Therefore, it appears that MIB-1 LI is a clinically useful prognostic parameter in nonfunctioning pituitary adenomas indicating probability of progression of postoperative tumor remnants, and MIB-1 LI may be indicative of invasiveness but is not a reliable predictor of recurrence.

Other markers for invasiveness appear to be matrix metalloproteinases (MMP) 2 and 9. MMP-2 was associated with aggressiveness and invasion in pituitary adenoma but was not related to tumor size or secretory function [36]. MMP-2 may thus be a useful marker for assessing the invasive potential. In another study [37], DNA microarray analysis of eight adenomas identified differentially expressed genes between invasive and noninvasive NFAs, revealing an eightfold increase in MMP-9 expression by gene clustering in human invasive NFAs, which was confirmed by other techniques, like real-time polymerase chain reaction, Western and Northern blot analyses, and immunohistochemistry. The activation of protein kinase C (PKC) increased by gene clustering in human invasive NFAs, revealing an eightfold increase in MMP-9 expression by gene clustering in human invasive NFAs, which was confirmed by other techniques, like real-time polymerase chain reaction, Western and Northern blot analyses, and immunohistochemistry. The activation of protein kinase C (PKC) increased both MMP-9 activity and expression, and was blocked by some PKC inhibitors. These results demonstrate that MMP-9 and PKC may provide putative therapeutic targets for the control of invasiveness. One study evaluated the expression of B-Raf mRNA and protein in pituitary adenomas, because certain mutations in the BRAF oncogene lead to constitutive activation of the Ras-mitogen-activated protein kinase (MAPK) pathway. Interestingly, overexpression of B-Raf mRNA and protein was found only in NFMA and not in functioning adenomas, implicating that overactivity of the Ras-B-Raf-MAP kinase pathway is involved in the pathogenesis of nonfunctioning adenomas [38].

Another intriguing new feature is the role of MEG3, a gene that is capable of stimulating p53-mediated transcription activation, thereby functionally controlling tumor suppression [39]. Specific loss of MEG3 expression was recently reported only in NFMA, but not in functioning adenomas, suggesting that MEG3 may play a critical role in control of tumor formation from this specific cell type [40]. In addition, an increased overall hypermethylation in the important regulatory regions of MEG3 gene (CpG methylation within the IG-DMR in the DLK1/MEG3 locus) was demonstrated in human NFMA only. This increased methylation contributes to loss of expression and antiproliferative function of this noncoding RNA gene, and may be an additional mechanism for MEG3 gene silencing, specifically in NFMA.

Another study evaluated the potential rationale for treatment of NFPAs with temozolomide. The cytotoxic effect of temozolomide is predominantly caused by methylation of the O6 position of guanine in DNA. The DNA repair enzyme O(6)-methylguanine DNA methyltransferase (MGMT) plays a crucial role in the removal of alkylating lesions induced by temozolomide. Withalm et al. studied MGMT expression in 45 patients and found that 50% of patients with progressive, regrowing NFMAs exhibited low MGMT expression, which implicates that temozolomide could be used in these patients as an alternative treatment approach [41]. Finally, the Notch3 pathway appears to play an important role in the progression of nonfunctioning pituitary adenomas. Maio et al. very recently reported overexpression of Notch3 mRNA and protein overexpression only in NFMA, implicating the Notch3 pathway as a molecular therapeutic target for their treatment [42].

7. Somatostatin and dopamine receptor subtype expression and the response to treatment

To date, the clinical results of treatment with somatostatin analogs and dopamine agonists in nonfunctioning adenomas are rather disappointing. Since 2002, a limited number of studies aimed to further characterize somatostatin receptor subtypes (sst) and dopamine agonist receptor subtypes in these adenomas in vitro. Taboada and colleagues found that sstr3 mRNA was highest in NFPAs, followed by SSTR2, while SSTR1, SSTR4, and SSTR5 transcripts were hardly detectable [43]. In vitro studies with selective sst1, sst2 and sst5 receptors agonists, SST/DA chimera and D(2)-dopamine receptor agonist bromocriptine affect the viability of some, but not all, clinically nonfunctioning pituitary adenomas. Surprisingly, the most effective compound of all appeared to be bromocriptine, available for the clinical use of hyperprolactinemia since 1974 [44]. Another report indicated that a specific SST/DA chimeric molecule, BIM-23A760 induced a dose-related suppression in the majority of primary cultured human NFPA cells [45]. Pivonello et al. [46] evaluated the expression of dopamine receptors and D(2) isoforms in relation with cabergoline treatment in 18 in clinically nonfunctioning pituitary tumors in vitro, and subsequently the in vivo response on tumor mass after 1 year of treatment in nine patients. D(2) receptor was expressed in 67% of cases. D(2long) was found in 50%, D(2short) in 17%, and both D(2) isoforms in 33% of cases. In vitro, inhibition of alpha-subunit concentration was found in 56% of cases and was associated with D(2) expression. In vivo, tumor shrinkage was evident in 56% of patients and was associated with D(2) expression. The expression of D(2short) rather than D(2long) isoform was associated with the most favorable response of the tumor to cabergoline treatment [46]. The in vitro response after sst2 and 5 analogs was evaluated using cell viability in 13 NFMA by Padova et al. [47]: Sst analog with high affinity for sst2 reduced cell viability by 20–80% in eight of 13 NFMA studies, all expressing the sst2. The inhibitory effect on cell viability of sst5 selective analog was 15–80% in 10 of 13 adenomas studied, all but three expressing the sst5. Corticostatin, however, effectively reduced cell viability in only six NFPAs.

Somatostatin analogues might also act synergistically with other agents, for instance by interfering with intracellular pathways that increase the effect of rapamycin. The sensitivity to rapamycin was tested using octreotide as a tool to decrease intracellular activated Ser(473)-phosphorylated Akt
(pAkt-Ser(473)) in NFMA that expressed sst2 [48]. Octreotide increased levels of phosphorylated insulin receptor substrate-1 that were suppressed by rapamycin, subsequently decreasing levels of pAkt-Ser(473). In addition, octreotide potentiated the antiproliferative effects of rapamycin in human nonfunctioning pituitary adenoma cells sensitizing tumor cells even to low rapamycin concentrations. Combined treatment of octreotide and rapamycin triggered G(1) cell cycle arrest, decreasing E2F transcriptional activity and cyclin E levels by increasing levels of p27/Kip1. Addition of octreotide to rapamycin thus enables sensitization of nonfunctioning pituitary adenoma cells to the antiproliferative effects of rapamycin.

8. Conclusions

All evidence for treatment and follow-up for nonfunctioning adenomas is based on observational studies. Transsphenoidal surgery remains the cornerstone of treatment of nonfunctioning pituitary macroadenomas. When compared to the microsurgical procedure, some, but not all studies, favor endoscopy when gross total tumor resection is considered as outcome parameter, but endocrinological outcome is not different. However, the endoscopic approach reduces operating time, hospital stay, perioperative morbidity and hospital stay, as well as patient discomfort. Radiosurgery results in a high and durable rate of tumor control, including in those previously treated by conventional radiotherapy, but the risk of developing new anterior pituitary deficits is comparable to the risk after conventional radiotherapy. In selected cases of residual tumor invading the cavernous sinus, pituitary transposition may reduce the incidence of radiation induced pituitary insufficiency but more studies with this new technique are needed. In selected patients with NFMA without visual field defects, a wait-and-see approach with frequent evaluation of visual fields can be proposed. In these patients, this seems to be a safe alternative for transsphenoidal surgery, without the risk of irreversibly compromising visual function.

Tumor progression in nonfunctioning pituitary adenomas is difficult to predict; of the classical markers of proliferation, the MIB-1 LI is a clinically useful prognostic parameter and is indicative of invasiveness but is not a reliable predictor of recurrence. To date, the potential contribution of other, non-classical markers for proliferation still requires further validation, and effective medical treatment strategies are not available. Intriguing new features in the pathogenesis of NFMA are the role of the MEG 3 gene, and the role of temozolomide and rapamycin as potential therapeutic targets, combined with octreotide. The contribution of chimeric sst-DA analogues on proliferation in vitro is promising but the effects of these molecules have not yet been evaluated in clinical trials with patients with nonfunctioning adenomas.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References
