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

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General introduction

CHAPTER 1

I. ANATOMY AND PATHOLOGY OF THE PITUITARY GLAND

The pituitary is a small neuro-endocrine organ with a diameter of only 1 centimetre, and a weight of about 0.5 gram. It is attached to the hypothalamus by the pituitary stalk and a portal system. The pituitary is composed of two morphologic and functional different components: the anterior lobe (adenohypophysis) and the posterior lobe (neurohypophysis). The adenohypophysis consists of five different endocrine cell types, identified by antibodies against pituitary hormones and capable of production and secretion of pituitary hormones:

1. Somatotroph cells. These cells are acidophilic and produce growth hormone (GH).
2. Lactotroph cells. These cells are acidophilic and produce prolactin.
3. Corticotroph cells. These cells are basophilic and produce adenocorticotrophic hormone (ACTH), pro-opiomelanocortin (POMC), melanocyte stimulating hormone (MSH) and endorphins.
4. Thyreotrophic cells. These cells are basophilic and produce thyrotrophin (TSH).
5. Gonadotrophic cells. These cells are basophilic and produce luteinising hormone (LH) and follicle-stimulating hormone (FSH).

The neurohypophisis produces the hormones oxytocin and arginine vasopressin (AVP).

II. PITUITARY TUMORS

Different lesions may present as a mass within the sella turcica. In unselected autopsy series, the prevalence of pituitary tumors varies between 2 and 27%, with an average prevalence of 11% in a compilated series of 12.411 patients (1-3). The prevalence of adenomas > 1.0 centimetres in these series is less than 1% (1-4). Moreover, in series of CT or MR-imaging, in 10-20% of all patients small pituitary tumors can be detected (5;6). The differential diagnosis of a sellar mass is shown in Table 1 (adapted from Post *et al* (7) and Sam *et al* (8))**.** The differentiation between the various conditions causing a pituitary mass can sometimes be difficult, because these tumors may share similar clinical presentation and radiological features.

In patients operated for pituitary tumors, pituitary adenomas account for more than 90% of the tumors (9). Of other causes, the most common diagnosis is Rathke's cleft cyste (28%), craniopharyngioma (14%), metastatic carcinoma (12%), chordoma (11%) and meningioma (10%) (9). The proportion of patients with functioning, respectively, nonfunctioning adenomas among patients with pituitary adenomas, is dependent on the applied selection criteria. In series of patients operated for pituitary tumors, 25-50% of the adenomas is nonfunctioning, 50-75% is functioning. Off all pituitary adenomas, 40%-50% is clinical nonfunctioning (3;10;11). In autopsy series, the vast majority being

Table 1. Differential diagnosis of sellar masses

Differential diagnosis of sellar masses
I Pituitary adenomas
Nonfunctioning adenomas
Functioning adenomas
Prolactinomas
Cushing's disease
Acromegaly
Thyreotroph adenomas
Gonadotroph adenomas
II Cystic lesions
Rathke's cleft cyste
Craniopharyngioma
Arachnoid cyst
III Neoplasms
Meningioma
Germ cell tumor
Chordoma
Granular cell tumor
Glioma
Metastatic lesions
Lymphoma
IV Inflammatory/infectious lesions
Sarcoidosis
Tuberculosis
Langerhans histiocytosis
Lymphocytic hypophysitis
Pituitary abcess
V Vascular lesions
Aneurysm

microadenomas, pituitary lesions turn out to be nonfunctioning adenomas in about 50%, the other 50% mainly being hormonal active adenomas (1;12). In contrast to microadenomas, in patients with macroadenomas there is no equal distribution between functioning and nonfunctioning adenomas, nonfunctioning adenomas accounting for over 80% of all pituitary tumors (13-16). The reason for this higher prevalence of nonfunctioning pituitary adenomas is given by the fact that functioning adenomas are characterized by hormone excess, giving rise to clinical symptoms in an earlier phase of tumor growth and development.

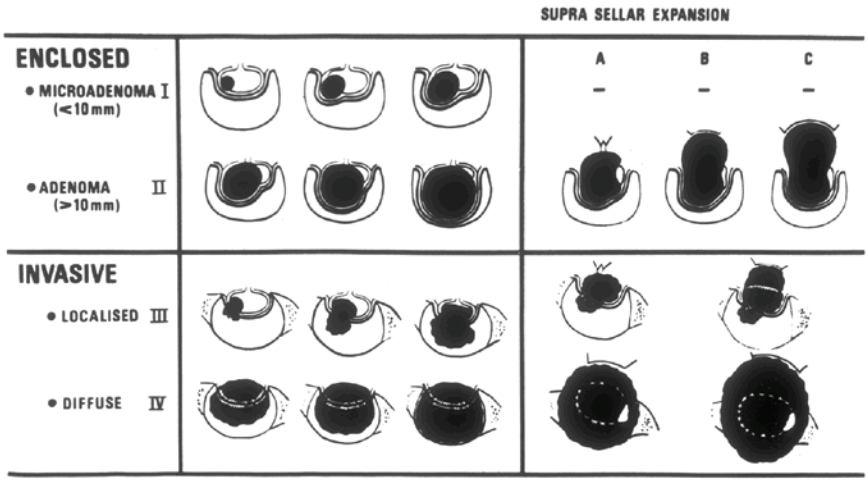
III. NONFUNCTIONING PITUITARY ADENOMAS

Pituitary adenomas

Pituitary adenomas are non-metastasing neoplasms of the pituitary, composed of adenohypophysal cells and lacking a true capsule (17;18). Pituitary adenomas are classified according to tumor size and to functionality. An adenoma with a diameter < 1 cm is defined as a microadenoma, an adenoma with a diameter > 1 cm as a macroadenoma. This differentiation between micro- and macroadenomas is clinically relevant, because, in contrast to microadenomas, macroadenomas may result in pituitary deficiencies and visual field defects. Pituitary tumors are staged according to the classification by Hardy and modified by Wilson (19). This classification is based on tumor diameter and local invasiveness (I-IV), and suprasellar/parasellar extension (A-E) (Figure 1).

Pituitary adenomas can be classified as either functioning or nonfunctioning according to their hormonal activity in vivo. Functioning adenomas are characterized by the overproduction of one, or in rare cases multiple, pituitary hormones. The hormonal activity of pituitary adenomas is usually a reflection of the underlying cytodifferentiation, which may consist of any of the cell types of the adenohypophysis. Nonfunctioning pituitary tumors are characterized by the absence of clinical and biochemical evidence of pituitary hormonal overproduction in vivo. Although from a clinical perspective nonfunctioning adenomas form a homogeneous group, from a pathological perspective they represent a heterogeneous group. By immunohistochemistry, the adenoma can be shown to consist of somatotroph, thyreotroph, lactotroph, gonadotroph or corticotroph cells, whereas adenomas also may contain multiple hormonal cells (20). Because nonfunctioning adenomas

Figure 1. Hardy-Wilson classification of pituitary tumors



Growth pattern of acidophilic adenomas.

lack clinical effects of hormone excess by definition, clinical nonfunctioning adenomas containing hormone producing cells are also referred to as silent pituitary adenomas. The most common silent adenomas are gonadotroph adenomas (20-22). These tumors contain immunoreactivity for α-subunits as well as β-subunits of LH and/or FSH. Adenomas that can not be classified according to immunohistochemistry are called null-cell adenomas. However, there is evidence that most cases of null-cell adenomas are gonadotroph adenomas with low expression of immunoreactivity of gonadotroph cells (21;23). Some null-cell adenomas may be composed of pluripotental progenitor cells, capable of differentiating to different hormone-producing cell lines (24).

The rare pituitary adenomas that do metastasize are mainly functional in origin (21). A malign course in nonfunctioning pituitary adenomas is extremely rare (25), although local invasion is a frequent observed phenomenon in clinically nonfunctioning adenomas (26-28).

Pathophysiology

Two different theories have been proposed to explain pituitary tumor-genesis. The first theory indicates hormonal stimulation as the initial event causing pituitary tumorgenesis. The second theory indicates an intrinsic pituitary defect as the initiating event.

Almost all pituitary adenomas, both functioning and nonfunctioning, are monoclonal in origin (3;29), whereas polyclonal pituitary adenomas are extremely rare (18). In normal female tissue one of two x-chromosomes is inactivated. This event occurs randomly, leading to polyclonality in normal tissue (3). In female patients with pituitary adenomas, monoclonality of the tumor was proven by the loss of heterozygosity in tumor tissue (29). This finding implies molecular alteration(s) as the underlying event for tumorgenesis and that pituitary adenomas arise from clonal expansion of a single mutated pituitary cell. Because of the monoclonality of the tumor, hypothalamus disorders, such as the overproduction of hypothalamic, proliferative hormones, do not seem to play an important initial pathophysiologic role in pituitary adenomas. This is established by the lack of associated hyperplasia in pituitary tissue surrounding pituitary tumors (17;18). However, although a genetic modification seems to be the initiating step, hormones and/or growth factors may play a role in promoting subsequent cell proliferation. The molecular events leading to adenoma formation are incompletely understood (30). Molecular studies have revealed that most of the mutations present in other malignancies, are usually absent in clinical nonfunctioning adenomas (18). Several genes and molecular mechanisms have been proposed to be involved. Deletions in the region 13q14 have been identified in pituitary adenomas, pointing towards a possible tumor suppressor gene at this locus (18). Loss of expression of p16 is probably involved in the pathogenesis of adenomas, particularly in null cell adenomas (31). Pituitary tumor transforming gene (PTTG) is found to be overexpressed in a wide range of pituitary adenomas, although its role in tumorgenesis is

unclear (3). However, at present, the relationship between these molecular changes and clinical phenotype is unclear.

Clinical presentation

The initial presentation of nonfunctioning pituitary adenomas depends largely on size and growth pattern of the tumor. In general, nonfunctioning microadenomas do not cause symptoms, because the tumor does not exceed the anatomical borders of the sella turcica, and pituitary function is preserved. However, even in about 15-20% of all patients with nonfunctioning macroadenomas, the tumor is discovered accidentally and not accompanied by clinical symptoms (32;33). The main presenting symptoms of nonfunctioning pituitary macroadenomas are headache, visual field defects and hypopituitarism due to mass effects of the tumor. Headache is present in about 40-50% of all patients (32;33) and can be caused by increased intracranial pressure and stretch of the dura mater (18). Visual disturbances are caused by compression of the optic chiasm. Typically, macroadenomas cause bitemporal field defects, explained by the anatomy of the visual pathways in the chiasm: the crossing inferonasal nerve fibres lie at the anterior part of the chiasm and are therefore compressed first. This causes the paradigmatic pattern of visual field defects: bitemporal defects of the upper quadrant. However, depending on the growth pattern of the tumor, there may exist asymmetry between the visual field defects of the two eyes. Visual field defects are present in the vast majority of all patients presenting with a pituitary macroadenoma (32;33).

Hypopituitarism is caused by three mechanisms: 1. compression of the pituitary stalk, which causes decreased availability of hypothalamic stimulatory hormones, 2. compression of functioning pituitary tissue, and 3. hypothalamic involvement of the pituitary tumor. In the majority of patients presenting with complaints of nonfunctioning pituitary macroadenomas, pituitary insufficiency is present to some degree (34-36). In addition to pituitary deficiencies, nonfunctioning macroadenomas can be accompanied by hyperprolactinemia. The secretion and release of prolactin is inhibited by hypothalamic dopamine-release. Pituitary tumors may disrupt dopamine release by compression of the pituitary stalk, and may therefore be accompanied by modest hyperprolactinemia. A prolactin level less than 100 µg/L is compatible with compression of the pituitary stalk (37;38).

Other presenting signs of pituitary macroadenomas, though occurring infrequently, are cranial nerve dysfunction, diplopia and apoplexy. Cranial nerve dysfunction can be caused by infiltrating pituitary tumors. Apoplexy is a clinical syndrome resulting from acute haemorrhage or infarction of the pituitary tumor (39). In unselected patients with nonfunctioning macroadenomas, apoplexy is the presenting sign in about 10-25% of the patients (33;40).

Treatment

The treatment of choice for pituitary adenomas complicated by visual field defects is transsphenoidal surgery. Visual recovery has been demonstrated in the first days after surgical treatment (41;42) and is caused by decompression of the visual pathways, leading to a restoration of signal conduction. Visual field defects and visual acuity improve in more than 80% of the patients after transsphenoidal surgery (33;43-45), although visual field defects and visual acuity may worsen in a limited number of patients after surgery (46-49).

The results of transsphenoidal surgery on pituitary function vary between different studies. Some studies report, to a variable degree, an improvement in pituitary function (45;50-53), whereas other studies could not demonstrate significant improvement in pituitary function (34;36;43) or even reported a decrease in pituitary function (35;54). Therefore, the aim of transsphenoidal surgery should be improvement of visual field defects, rather than improvement of pituitary function.

During long-term follow-up after transsphenoidal surgery, tumor recurrence is observed in 12-46% of the patients (43;44;55;56). The role of postoperative radiotherapy, in order to prevent tumor recurrence, is still under debate. Some centers provide postoperative radiotherapy in a selection of the patients to prevent tumor regrowth (35;36;56;57). Nonetheless, even after postoperative radiotherapy, tumor recurrence was reported in 2-36% of the irradiated patients (36;44;55;56). The possible benefit of postoperative radiotherapy, *i.e.* a decrease in long-term growth rate of pituitary adenomas, has to be balanced against potential side effects of radiotherapy such as hypopituitarism (58-60) and secondary brain tumors (61).

Mortality

Pituitary adenomas are accompanied by considerable morbidity. In macroadenomas morbidity is caused by mass effects of the tumor leading to visual field defects, decreased visual acuity and pituitary insufficiency in the majority of patients (32;33). In acromegaly and Cushing's disease, morbidity is caused by hormonal overproduction, in addition to tumor mass effect in cases of macroadenomas. In Cushing's disease, cortisol excess causes central obesity, insulin resistance, hypertension and osteoporosis (62). Moreover, cortisol overproduction is associated with increased cardiovascular risk, continuing even after remission of the disease (63). In acromegaly exposure to growth hormone excess is associated with pathological conditions such as hypertension, cardial hypertrophy, diastolic dysfunction, insulin resistance, sleep apnea and ventilatory dysfunction (64;65). In patients with functioning pituitary adenomas (66;67), nonfunctioning pituitary adenomas (68) as well as craniopharyngiomas (69), an increased standardized mortality ratio (SMR) have been reported. Moreover, in several studies, an increased SMR in patients with hypopituitarism has been reported (68;70-72). In the majority of studies the general

population was used as control group to assess mortality in patients with pituitary adenomas. However, it is presently unknown to what extent the excess mortality is caused by pituitary tumors and their treatment in general, and to what extent (previous) by previous overexposure to cortisol or growth hormone.

Quality of life assessment

The assessment of Quality of Life (QoL) has increasingly become an important tool to assess the effects of disease and outcome of medical treatment. Quality of life refers to the patient's perception of their physical, mental and social health. For numerous diseases and treatment modalities quality of life has been investigated (73-80). In general, pituitary diseases are associated with impaired QoL (81). This can be explained by several factors. Macroadenomas are associated with different degrees of hypopituitarism, which require hormonal substitution. However, despite optimal endocrine replacement strategies, normal endocrine function can not be perfectly restored by exogenous substitution. It is likely that this contributes to impaired QoL parameters in hypopituitarism. Moreover, growth hormone and ACTH producing adenomas induce irreversible effects through the syndromes of acromegaly (82) and Cushing's disease (83), which persist despite long-term cure of the disease. Finally, radiotherapy for pituitary tumors is associated with decreased QoL (82).

IV. SCOPE OF THIS THESIS

In this thesis, the following important clinical aspects of the treatment of nonfunctioning pituitary macroadenomas will be addressed:

- The natural course of nonfunctioning pituitary macroadenoma
- Long-term outcome after transsphenoidal surgery
- Pattern of improvement in visual acuity after transsphenoidal surgery
- Mortality in patients with pituitary adenomas
- Quality of Life assessment

The natural course of nonfunctioning pituitary macroadenoma

Because the majority of patients with NFMA are operated, the natural course of NFMA is largely unknown. In **chapter 2** we present the outcome of a study, designed to estimate the natural course of NFMA in non-operated patients. Studies on the natural course of nonfunctioning macroadenomas are important, not only because they fill a gap in common knowledge. Until now, the majority of patients with a nonfunctioning macroadenoma will be operated in most centers, even in the absence of visual field defects (84). However,

more detailed knowledge of the natural course of nonfunctioning pituitary macroadenomas may select patients in whom a conservative approach is more appropriate.

Long-term outcome after transsphenoidal surgery

Transsphenoidal surgery is the golden standard in the treatment of nonfunctioning pituitary macroadenomas with visual field defects. However, the role of postoperative radiotherapy is still under debate. Prospective trials evaluating the effect of postoperative radiotherapy on regrowth rates of NFMA have not been published. Only 2 studies have been published in consecutive NFMA patients with a wait and see policy after transsphenoidal surgery (32;43). However, these reports do not propose a wait-and-see policy for all NFMA patients.

In **chapter 3** we present the results of a treatment strategy in which postoperative radiotherapy was not applied in consecutive patients after transsphenoidal surgery. The main question was whether a treatment strategy without postoperative radiotherapy may lead to good tumor control, without adversely affecting patient's outcome. A wait-and-see policy after transsphenoidal surgery would have the advantage to postpone the possible side effects of radiotherapy in patients with tumor recurrence for several years.

Pattern of improvement in visual acuity after transsphenoidal surgery

One of the main goals of surgical treatment in nonfunctioning macroadenomas, is the restoration of visual function. The process of recovery of visual field defects starts immediately after surgery and can already be documented on the second postoperative day (41). This process of recovery is probably due to restoration of the velocity of conduction in the optic nerves. However, improvement of visual field defects appears to continue even years after initial surgical treatment (42;85). This second, slow phase of recovery may reflect restoration of axonal transport and remyelination.

The process of gradual visual improvement, has only been studied for visual field defects, not for visual acuity (42). In **chapter 4** we present data on the pattern of recovery of visual acuity until one year after transsphenoidal surgery for nonfunctioning pituitary macroadenoma.

Mortality in patients with pituitary adenomas

An increased SMR has been reported in both hypopituitarism and pituitary tumors (68). However, it is presently unknown to what extent the excess mortality is caused by pituitary tumors and their treatment in general, and to what extent by (previous) exposure to cortisol or growth hormone overproduction.

In **chapter 5** we describe a single centre study to assess mortality ratios during long term follow up after transsphenoidal surgery in patients with nonfunctioning pituitary macroadenomas and Cushing's disease. To answer to the question to which extent previ-

ous exposure to hormonal overproduction *per se* is associated with increased mortality, we compared mortality in patients operated for Cushing's disease to mortality in patients operated for nonfunctioning pituitary macroadenomas.

Quality of Life assessment

Although quality of life has been investigated in patients with functioning pituitary tumors (83;86), no studies on QoL in patients treated for nonfunctioning adenomas, compared to healthy controls, have been published. Most studies on QoL in pituitary diseases were not focussed on nonfunctioning tumors, but included heterogeneous groups, consisting of both functioning and nonfunctioning pituitary tumors (87-90). In **chapter 6** we present the results of a quality of life assessment in adult patients treated by transsphenoidal surgery for nonfunctioning macroadenomas. In **chapter 7** we present the same assessment in adult patients treated for craniopharyngioma.

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