Prolactinomas : clinical studies

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Prolactinomas

CLINICAL STUDIES

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ISBN 978-90-8559-376-8

Publication of this thesis was financially supported by Ferring, Ipsen, Merck Sharp & Dohme, Novartis Oncology, Novo Nordisk, Pfizer, Sanofi-Aventis, Servier, Will-Pharma.

Cover photo: Andrew Beierle
Cover design: Maarten Houwer and Mieke Kars

Lay-out and print: Optima Grafische Communicatie, Rotterdam

PROLACTINOMAS

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Proefschrift

ter verkrijging van

de graad van Doctor aan de Universiteit Leiden,

op gezag van Rector Magnificus prof.mr. P.F. van der Heijden,

volgens besluit van het College voor Promoties

te verdedigen op woensdag 10 september 2008

klokke 15.00 uur

door

Marleen Kars

geboren te Oudewater

in 1975

PROMOTIECOMMISSIE

Promotores:	Prof.dr. J.A. Romijn
	Prof.dr. J.W.A. Smit
Copromotor:	Dr. A.M. Pereira Arias
Referent:	Prof.dr. E. Fliers, Academisch Medisch Centrum, Amsterdam
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Chapter 1

INTRODUCTION

INTRODUCTION

Prolactinomas are adenomas derived from lactotroph cells of the pituitary gland, and are characterized by hypersecretion of prolactin. Prolactin release and production is inhibited by dopamine, originated from the hypothalamus. Normal prolactin levels in women and men are, depending of the assay used, but overall below 25 µg/L and 20 µg/L, respectively (1). Prolactinomas are classified according to their diameter into microprolactinomas (<10 mm in diameter), macroprolactinomas (≥10 mm in diameter), and giant prolactinomas (>40 mm in diameter).

This thesis focuses on several clinical manifestations of micro- and macroprolactinomas. This introductory chapter provides an overview of the pathophysiology of prolactin secretion and prolactinomas.

1. Prolactin

Prolactin was identified by French researchers in 1928, who discovered that prolactin was capable of inducing milk secretion in rabbits (2). The primary action of prolactin is stimulation of lactation after delivery. However, prolactin has more actions than all other pituitary hormones combined. Furthermore, prolactin is only for a part produced by the lactotroph cells in the anterior pituitary gland. The greatest part of prolactin is produced outside the pituitary gland (extrapituitary prolactin). Prolactin may act as a hormone, by the classic endocrine pathway, as a growth factor, neurotransmitter, or immunoregulator, in an autocrine or paracrine manner. In various vertebrates, prolactin receptors are widely distributed.

Prolactin binds to cell surface receptors of the class 1 cytokine receptor superfamily, which entail a single-pass transmembrane chain. This binding of prolactin to its receptor is a two-step process, in which site one of the prolactin molecule binds to one receptor molecule, after which a second receptor molecule binds to site two of the prolactin molecule, forming a homodimer consistingof one molecule of prolactin and two receptor molecules (2). Dimerization of the receptor induces tyrosine phosphorylation and activation of the JAK kinases, followed by phosphorylation of the receptor. So far, more than 300 distinct actions of prolactin have been reported, including effects on water and electrolyte balance, growth and development, brain and behaviour, immune regulation, metabolism and adrenal steroidogenesis, and reproduction (2).

Prolactin secretion exhibits diurnal variation, with higher amplitudes of pulses occurring after onset of sleep, especially during the non-rapid eye movement periods. It is believed that these diurnal changes are sleep induced, rather than driven by an inherent diurnal rhythm (3).

2. Causes of hyperprolactinemia

Hyperprolactinemia can be caused by physiological processes, pharmacological effects, and pathological effects. Physiological causes of hyperprolactinemia include pregnancy, physical or psychological stress, and breast stimulation (Fig. 1). Medication, stimulating dopamine

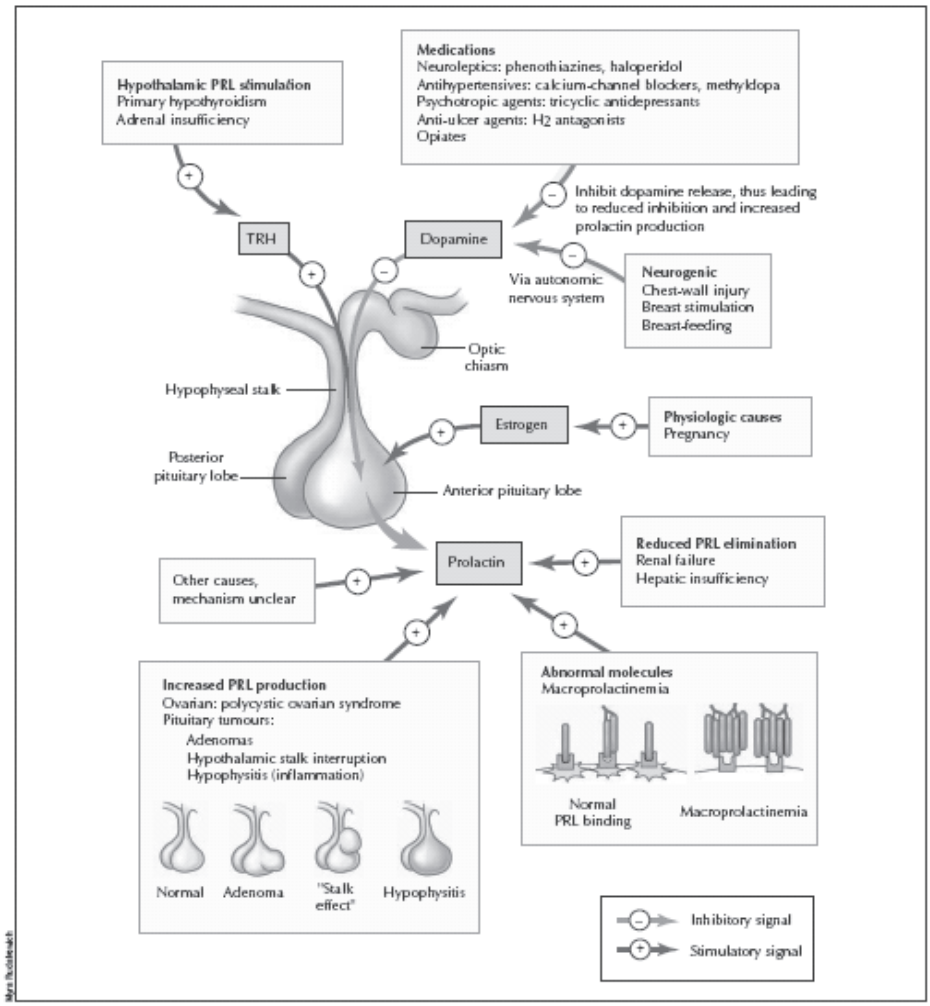

Figure 1. Causes of hyperprolactinemia

Prolactin (PRL) is under dual control from the hypothalamus, where dopamine serves as an inhibitory signal, preventing PRL secretion. Conditions that result in impaired dopamine delivery or enhanced TRH signaling, or both, result in increased PRL release.

Adapted from Serri O. *et al*., Diagnosis and management of hyperprolactinemia, in *Canadian Medical Association Journal* 2003;169(6):575-581.

receptors on lactotroph cells (for example metoclopramide, phenothiazides) or inhibiting dopamine release from the hypothalamus (for example monoamine oxidase inhibitors, tricyclic antidepressants, serotonin re-uptake inhibitors), induce hyperprolactinemia. In general, medication induced hyperprolactinemia is associated with levels up to 100 µg/L (4). Compression of the pituitary stalk due to suprasellar extension of craniopharyngioma, meningeoma, nonfunctioning adenoma, or severe head trauma can disrupt dopamine transport in the portal

vessel, and may lead to hyperprolactinemia, with levels mostly not exceeding 200 µg/L. Furthermore, primary hypothyroidism can cause hyperprolactinemia due to increased synthesis of thyrotropin-releasing hormone (TRH), stimulating prolactin secretion. Other conditions capable of increasing prolactin levels are chronic renal failure and liver cirrhosis. Finally, hyperprolactinemia can be caused by prolactinomas.

High levels of prolactin can also sometimes be explained by macroprolactinemia. Macroprolactinemia is caused by the presence of elevated levels of prolactin of high molecular mass, mostly due to monomeric prolactin with an immunoglobulin complex (prolactin-autoantibody complex), which has no bioactivity. Depending the immunoassay used, macroprolactinemia accounts for up to 25% of biochemically documented hyperprolactinemia (5). This indicates that macroprolactinemia represents a common diagnostic pitfall. Consequently, hyperprolactinemia detected for the first time, especially in the absence of symptoms (*e.g.* in the presence of normal menstrual cycles), sera should routinely be treated with polyethylene glycerol (PEG) to establish macroprolactin. In macroprolactinemia, the prolactin levels in hyperprolactinemic sera after PEG precipitation will fall to normal levels.

3. Epidemiology of prolactinomas

Prolactinomas are the most frequent pituitary adenomas, and account for approximately 40% of all pituitary adenomas, with an estimated prevalence of 60-100 per million population (6). However, recently, Daly *et al*. found a much higher prevalence in Belgium of 62 per 100.000 inhabitants (7). Microprolactinomas, rarely (*i.e.* in less than 5% of the cases) increasing in size, account over 90 percent of all prolactinomas, and occur most frequently in women, between the age of 20 and 50 years (4). One possible explanation for this increased prevalence of prolactinomas in women is that the symptoms of hyperprolactinemia become more readily evident, such as amenorrhea and galactorrhea, and secondary infertility. Men may ignore the symptoms of impotence and decreased libido, and seek attention to their general practitioner when signs of compression of adenoma, such as headache and visual field defects, develop. Furthermore, in some cases, prolactinomas are found as incidentalomas (8;9).

4. Clinical presentation of prolactinomas

Prolactinomas cause gonadal and sexual dysfunction related to hyperprolactinemia, and symptoms related to tumor expansion. The most common symptoms of hyperprolactinemia in premenopausal women are amenorrhea and galactorrhea. Some women may present with irregular menses (oligomenorrhea), or even with regular menses. Amenorrhea is often detected after discontinuation of the use of oral contraceptive or after pregnancy. The majority of women present with microprolactinomas. In contrast, most men present with macroprolactinomas and complaints of headache, visual disturbances, or cranial nerve dysfunction. Furthermore, men have complaints of hyperprolactinemia, such as impotence, decreased libido and beard

growth. Gynaecomastia and galactorrhea are uncommon. At last, most men and women have complaints of weight gain.

Macroprolactinomas typically present with prolactin levels over 200 µg/L. A discrepancy between a large pituitary adenoma and mildly elevated prolactin level may be due to either compression of the pituitary stalk by a nonfunctioning macroadenoma or a so called "high dose hook effect" of the assay for prolactin, which caused an extreme underestimation of prolactin levels. This artefact can be eliminated by serial dilution of the serum samples.

At presentation, none of the patients with microprolactinomas have pituitary deficiencies, apart from suppressed gonadotropins (10;11). Hyperprolactinemia causes hypogonadotropic hypogonadism in men and women due to inhibitory effect of high prolactin levels on hypothalamic gonadotropin-releasing hormone (GnRH) release. In patients with macroprolactinomas, hypopituitarism, other than hypogonadism, vary between 29 and 59%, and is overall slightly more present in men compared to women (10-13).

Suprasellar extension of the adenoma often compresses the optic nerves and classically results in bitemporal hemianopia and diminished visual acuity. Visual field defects, assessed by Goldmann-Friedmann perimetry, are present in 22-48% of the patients with macroprolactinomas (10-12;14;15). Similar to hypopituitarism, visual field defects are slightly more prevalent in men compared to women (10). None of the patients with microprolactinomas have visual field defects at presentation (10;11).

5. Pathogenesis of prolactinomas

Hypotheses concerning the pathogenesis of prolactinomas, are altered dopamine regulation (dopaminergic receptor or postreceptor dysregulation) and local somatic mutations (3). Observations arguing against the first hypothesis are, that dopamine deficits due to neuroleptics or pituitary stalk compression do not induce prolactinomas, most adenomas are confined to a portion of the pituitary gland rather than characterized by widespread hyperplasia, and a low recurrence after primary cure of adenoma. The local mutation hypothesis is based on X-chromosomal inactivation analysis, showing that almost all human pituitary adenomas are monoclonal (3). However, specific mutations underlying prolactinomas remain to be established, with the exception of genetic syndromes like MEN 1 syndrome, which is also associated with prolactinomas.

6. Treatment of prolactinomas

Therapy of prolactinomas is aimed at:

1) reduction of prolactin levels, and its clinical consequences such as gonadal dysfunction, infertility, and osteoporosis,
2) reduction of tumor mass, thereby relieving visual field defects, and possibly hypopituitarism,
3) preservation of residual pituitary function,

4) prevention of recurrence/regrowth of tumor mass, and

5) improvement of quality of life.

Treatment goals of micro- and macroprolactinomas are similar, although in the case of macroprolactinomas more emphasis of the therapy is focussed on control of tumor size.

6.1. Medical treatment of prolactinomas

Medical therapy with dopamine agonists is the initial treatment of choice in all prolactinomas. These drugs inhibit prolactin secretion and reduce tumor volume. Dopamine agonists most commonly used are ergot-derived dopamine agonists bromocriptine and cabergoline, and non-ergot derived dopamine agonist quinagolide. Dopamine agonists have a wide spectrum of pharmacological actions at different receptor sites (16). Therefore, it is not surprising that these drugs display a number of side effects. The secretion of prolactin is mainly regulated by the inhibitory tone exerted by hypothalamic release of dopamine. Dopamine inhibits prolactin secretion through D2 dopamine receptors, expressed by normal and tumorous lactotroph cells of the pituitary.

More than 25 years ago, bromocriptine was introduced into clinical practice as the first medical treatment for prolactinomas. It has a relatively short elimination half-life, and consequently it has to be taken 2-3 times a day in dosages ranging from 2.5 to 15 mg/day. For microprolactinomas, bromocriptine is capable of normalizing prolactin levels, restoring gonadal function, and inducing tumor shrinkage in about 60-80% of the patients (12;17;18). For macroprolactinomas, bromocriptine is effective in only 50-70% of patients (12;19;20). Disadvantages of bromocriptine treatment are the frequent occurrence of side effects, leading to interruption of therapy in 12% of the patients, according to reports by Webster *et al*. (17;21). Tumor regrowth after discontinuation has been reported, although data on this issue are scarce (22).

The non-ergot derived dopamine agonist quinagolide has a longer half-life and is taken only once daily. It is effective in normalisation of prolactin levels (in 70-100% of the patients with microprolactinomas, and in 67-88% of the patients with macroprolactinomas), fertility, and to induce tumor shrinkage (in 55% of the patients with microprolactinomas, and in 75% of the patients with macroprolactinomas) (23-29). Therefore, quinagolide seems to be slightly more effective than bromocriptine, and it is associated with less side effects compared to bromocriptine (23;25).

At present, cabergoline is the preferred dopamine agonist in the treatment of prolactinomas. Cabergoline is a potent agonist of the D2 dopamine receptor, and, in general, the mean starting dosage is 0.25-0.5 mg twice a week. In microprolactinomas, the average dosage is 0.5 mg/week, and in macroprolactinomas 1 mg/week. Several studies have demonstrated the efficacy of cabergoline in normalizing prolactin levels, and inducing tumor shrinkage, especially in macroprolactinomas. Normal prolactin levels are accomplished in 75-90% of the patients with micro- or macroprolactinomas, and an average decrease in tumor volume of 72-92% is reported (11;14;15;17;30;31). Even in patients with resistance to other dopamine agonists, cabergoline

has proven to be effective (14). Furthermore, cabergoline seems to induce much fewer and less severe side effects than other dopamine agonists, since only 3-4% of the patients had to discontinue treatment (15;17).

6.2. Surgical treatment of prolactinomas

In some patients medical treatment does not result in adequate treatment of micro- and macroprolactinomas. This can be due to intolerance to dopamine agonists, which occurs even in some patients using cabergoline. In other patients, there may be resistance to the effects of dopamine agonists. In these patients, surgery is a second line option.

Success rates of transsphenoidal surgery differ between micro- and macroprolactinomas. Furthermore, surgical success rates are highly dependent upon the experience of the neurosurgeon. For microprolactinomas, surgery initially restores prolactin levels in 85-90% (32-36). For macroprolactinomas, especially with parasellar extension, transsphenoidal surgery is less successful. Initial surgical remission rates, *i.e.* normalized prolactin levels, vary between 18-80% (33;35-37). A review of Gillam *et al*., combining data of 45 series (n=2137) in microprolactinomas, and 39 series (n=2226) in macroprolactinomas, reports initially remission rates of 75% and 34%, respectively (22). From the same series, long-term recurrence rates are 18% for microprolactinomas, and 23% for macroprolactinomas. Prolactin levels, measured one day after surgery, predict long-term cure (38).

An adverse effect of transsphenoidal surgery is the induction of hypopituitarism. Although data concerning this subject is scarce, two comprehensive studies of transsphenoidal surgery in large series of patients with pituitary adenomas report pituitary deficiencies of one or more axis in 3% of the patients after surgery (35;36). The first study reports long-term outcome after 10 years of follow-up in 4020 patients with pituitary adenoma, of which 1180 patients with prolactinomas (35). The second study describes results of transsphenoidal surgery in 1140 patients with pituitary adenomas (151 patients with prolactinomas) after 4 years of follow-up (36). The overall mortality rate following transsphenoidal surgery is less than 0.5% (35;36). Major morbidity (cerebrospinal fluid leak, meningitis, stroke, intracranial hemorrhage, and visual loss) occurs in 1-2% of the patients, whereas minor complications (sinus disease, nasal septal perforation, epistaxis, wound infections, and hematomas) occur in approximately 6.5% of the patients (35;36).

6.3. Postoperative radiotherapy of prolactinomas

Radiotherapy has limited role in the treatment of prolactinomas. In most cases, radiotherapy is applied after failed transsphenoidal surgery or, rarely, after only medical therapy. Therefore, in general it is considered as a third line therapy, after failure of medical treatment and after transsphenoidal surgery. In series of patients with unsuccessful transsphenoidal surgery, conventional, fractionated radiotherapy normalized prolactin levels in approximately 34% (22).

Hypopituitarism can be induced both by surgery and radiotherapy, with a cumulative risk after postoperative radiotherapy of approximately 50% at 10-20 years (39;40).

In conclusion, the efficacy of medical therapy, especially of cabergoline, has limited the indication for surgery. Surgery is reserved for patients with intolerance or resistance to dopamine agonists. Multimodal therapy containing pretreatment with dopamine agonists, surgical debulking, and subsequent adjuvant radiotherapy may be necessary for giant or invasive prolactinomas. Against this background, we performed a retrospective study of the long-term outcome of multimodality treatment of all consecutive patients with a macroprolactinoma, initially treated with dopamine agonists (**chapter 2**).

7. Long-term outcome of treatment of prolactinomas

7.1. Remission after withdrawal of dopamine agonists

Withdrawal of bromocriptine results in recurrent hyperprolactinemia in almost all patients, up to 50-90% (41-43). Di Sarno *et al.* reported recurrence of hyperprolactinemia after one year of treatment with quinagolide in 100% of patients with micro- and macroprolactinomas (23). Other studies concerning the effects of withdrawal of quinagolide are not available. In the past 10-15 years, wide variations in remission rates have been reported after withdrawal of cabergoline, with a range of 10-69% (Table 1) (13;23;30;43-45). Colao *et al*. evaluated withdrawal of cabergoline (median duration of therapy 36-48 months) in 200 patients with nontumoral

Table 1. Literature review on cabergoline withdrawal

	Ferrari *et al.* (30)	Muratori *et al.* (44)	Cannavo *et al.* (45)	Di Sarno *et al.* (23)	Colao *et al.* (13)	Biswas *et al.* (43)	Our data
Year of publication	1992	1997	1999	2000	2003	2005	-
No. of patients	127	26	37	39	200	67	21
M/F, *No.*	3/124	-/26	5/32	8/31	44/156	NA	3/18
Macroprolactinoma, *No.*	19	-	11	16	70	-	5
Microprolactinoma, *No.*	71	26	26	23	105	67	16
Non-tumoral, *No.*	37	-	-	-	25	-	-
Pretreatment, *No.*	5 surg	3 surg, 18 DA	-	6 surg, 39 DA†	-	-	DA
Duration of cabergoline, *months*	14*	12	24	12	36-48*	36*	52*
Normal PRL, *%*	90	96	92	92	100‡	NA	100‡
Duration of follow-up, *months*	12	38-60	12	12	36-48*	12	16*
Normal PRL at follow-up, *No. (%)*	10/32 (31)	8/21 (38)	5/27 (19)	4/39 (10)	137/200 (69)	21/67 (31)	7/21 (33)

Data are expressed as mean, unless otherwise mentioned. M, male; F, female, PRL, prolactin; NA, not available; surg, transcranial or transsphenoidal surgery; DA, dopamine agonist other than cabergoline.

* Median

† Intolerant for bromocriptine, 12 months of quinagolide

‡ Inclusion criteria

hyperprolactinemia (n=25), microprolactinomas (n=105), or macroprolactinomas (n=70) (13). Recurrence rates of hyperprolactinemia after median follow-up of 12-18 months were 24% in nontumoral hyperprolactinemia, 30% in microprolactinomas, and 36% in patients with macroprolactinomas. In this prospective study, normal prolactin levels and tumor shrinkage of 50% or more on MRI were stringent conditions before cabergoline withdrawal. Recently, an observational study of this same study group, reported predictors of hyperprolactinemia after cabergoline withdrawal in 221 patients with prolactinomas, including 79 patients with macroprolactinomas (46). Only nadir prolactin levels during cabergoline use, and tumor size at the moment of cabergoline withdrawal predicted remission of hyperprolactinemia.

In conclusion, withdrawal of cabergoline after duration of therapy of 3-5 years can be attempted, especially if imaging has demonstrated tumor shrinkage of 50% or more. Although remission is reported in 60-70% of patients with prolactinomas, periodic assessment of prolactin levels, for example every 3 months the first year, would be advisable. In macroprolactinomas, dopamine agonist therapy should be reinstituted whenever hyperprolactinemia occurs, whereas in microprolactinomas an expectant approach can be followed.

7.2. Safety of dopamine agonists

Adverse effects of dopamine agonists can be grouped into three categories: gastrointestinal, neurological, and cardiovascular side effects. Symptoms tend to occur after the first dose and after increases of the dosage, but can be minimized by introducing the drug at low dosage at bedtime. The most common gastro-intestinal effects are nausea and vomiting. The most frequent neurological adverse effects are headache and drowsiness. Psychiatric adverse effects, such as psychosis or exacerbation of pre-existing psychosis, are infrequent and entirely remitted when the drug is discontinued (22). However, mood alterations, such as anxiety and depression, occur frequently. Dopamine agonists pergolide, bromocriptine, and recently cabergoline, used in the treatment of Parkinson's disease, have been shown to increase the risk of valvular heart disease and to induce retroperitoneal and pulmonary fibrosis (47-58). However, these adverse effects appear to be dose-dependent and in the treatment of prolactinomas only modest doses of dopamine agonists are used. To assess the prevalence of valvular heart disease in patients treated by dopamine agonists for prolactinomas, we compared echocardiographic data between patients with prolactinomas treated with dopamine agonists and control subjects in **chapter 3.**

7.3. Resistance of dopamine agonist

Varying definitions of dopamine agonist resistance are used. Molitch has proposed to use a uniform definition, defining dopamine agonist resistance with respect to prolactin levels as the failure to achieve normoprolactinemia, and with respect to tumor size as the failure to achieve tumor size reduction of 50% (59). The obvious candidate for a molecular alteration leading to dopamine agonist resistance is the lactotroph D2 dopamine receptor itself. Thus far, mutations

in the D2 receptor have not been identified in human prolactinomas. There is experimental evidence that some resistant prolactinomas have a reduced density of D2 receptors (60;61). Furthermore, special interest has also been focused on differences in the proportion of different isoforms of the D2 dopamine receptor (short and long), because the proportion of mRNA of the short D2 receptor proved to be lower in resistant prolactinomas compared to responsive prolactinomas (61).

The prevalence of resistance of prolactinomas to dopamine agonists differ between specific dopamine agonists, macro- or microprolactinomas, and initially or previously treated prolactinomas. Overall, resistance with respect to normalization of prolactin levels and tumor shrinkage can be expected in 25-50% of patients taking bromocriptine, and in 5-15% taking cabergoline (59). Possible treatment options for patients with dopamine agonist resistance are to increase the dosage or to switch to another dopamine agonist, transsphenoidal surgery, and/or radiotherapy.

7.4. Pregnancy

Prolactinomas present mainly in young women, and hyperprolactinemia results in suppressed gonadotropins, and as a consequence are an important cause of infertility. Furthermore, two major issues arise in the treatment of prolactinomas and pregnancy:

- effect of pregnancy on prolactinomas, and the possibility of growth of prolactinomas,
- effect of dopamine agonists on foetal development.

During pregnancy, estrogens stimulate prolactin synthesis and secretion, and promote lactotroph cell hyperplasia. Throughout pregnancy, there is an increase of the pituitary volume up to 136%, beginning in the second month of gestation (62). After delivery, the pituitary rapidly involutes and returns to its normal size by 6 months postpartum. According to data collected by Gillam *et al*., five studies have reported data on the risk of symptomatic tumor enlargement in pregnant women with prolactinomas (22). According to these data, risk of tumor enlargement for microprolactinomas is only 3% (12 of 457 pregnancies), and for previously not operated macroprolactinomas 32% (45 of 142 pregnancies). Surgical intervention was necessary in 12 of these 142 cases (8%). In 5 patients with microprolactinomas, and 17 patients with macroprolactinomas, dopamine agonist bromocriptine was reinstituted.

Most women diagnosed with prolactinomas will require treatment of hyperprolactinemia to ovulate and conceive. Therefore, it is likely that the foetus will be exposed to dopamine agonist treatment, for at least 3-4 weeks of gestation. All dopamine agonists have been shown to cross the placenta in humans. The use of bromocriptine, taken the first few weeks of gestation, has not been associated with an increase of spontaneous abortions, premature delivery, or congenital malformations in a very large number of pregnancies (n=6239) (22). Childhood development was analyzed in 64 children, without adverse effects. Considerable fewer data is available on the effects of bromocriptine used throughout the whole gestation. Although data on the safety of quinagolide during pregnancy are scarce, in a review of 176 pregnancies,

spontaneous abortions occurred in 14%, and there was one ectopic pregnancy, one stillbirth (at 31 weeks of gestation), and nine cases of malformations (21). Therefore, quinagolide should not be used if pregnancy is desired. Experience with the use of cabergoline in the first weeks of pregnancy is accumulating, and data of exposure to 350 cases have been reported without an increased percentage of spontaneous abortion, premature delivery, or congenital malformations (22). Recently, Colao *et al*. reported data of 329 pregnancies in women during the use of dopamine agonist cabergoline (63). Spontaneous abortions occurred in 9%, and there were 8 cases of stillbirths (3%), and 23 cases of neonatal major and minor abnormalities (7%). The incidence of spontaneous abortion in the general Europe population is approximately 11% (64). Major neonatal abnormalities are estimated at 6% worldwide (63). Bromocriptine would be advisable as the first treatment option of hyperprolactinemia and fertility. For women who are intolerant to bromocriptine, cabergoline is a reasonable second choice.

The follow-up of women with microprolactinomas during pregnancy includes withdrawal of dopamine agonist at the moment pregnancy is established. Periodic assessment of prolactin levels is not useful, due to the physiological rise during pregnancy. Routine periodic visual field testing and/or MRI are not cost effective, considering the low incidence of tumor enlargement. Therefore, visual field testing and/or MRI should be assessed when symptoms of mass effects, such as headache or visual disturbances, occur. If tumor enlargement is confirmed, reinstitution of dopamine agonist bromocriptine is often sufficient in reducing size. However, persistent visual field defects may necessitate transsphenoidal surgery.

In women with macroprolactinomas, one should consider carefully if dopamine agonists should be withdrawn or continued. The extend of para-/suprasellar extension of the macroprolactinomas and its relation with optic chiasma/nerves will be important for the decision. Furthermore, careful follow-up with 1-3/month visual field testing is advisable. MR imaging is reserved for patients with symptoms of tumor enlargement and/or progressive or new visual field defects. Again, if tumor enlargement is confirmed, reinstitution of dopamine agonist bromocriptine is preferable than surgery to mother and child, and transsphenoidal surgery is reserved for women who do not response to bromocriptine and vision is progressively worsening.

In conclusion, growth of (macro)prolactinomas during pregnancy is due to the withdrawal of dopamine agonists and stimulatory effects of high estrogens levels. Bromocriptine is the first line of therapy to treat hyperprolactinemia, adenoma and fertility in women, and can be withdrawn in women with microprolactinomas. Careful follow-up during pregnancy is especially warranted for women with macroprolactinomas.

7.5. Bone mineral density

Patients with prolactinomas are susceptible to develop osteopenia and osteoporosis. The prolactinoma-related bone loss is related to the period of secondary hypogonadism before the diagnosis of prolactinoma is established and treatment is started. Prolactinomas are more

prevalent at young age, and, therefore, peak bone mass can be affected in young patients with prolactinomas. In a cross-sectional study of 45 women with prolactinomas, 22% had Z-scores of bone mineral density measured with dual energy X-ray absorptiometry (DEXA) below the expected range for age in one or more sites (65). Furthermore, in 15% of men with prolactinomas osteoporosis of the lumbar spine had occurred (66). In most men and women with hyperprolactinemia, bone loss is reversed, or at least interrupted, once prolactin levels and gonadotropins are normalized. This indicates the importance of adequate disease control, *i.e.* normoprolactinemia is acquired to prevent long-term complications.

7.6. Quality of life

Endocrine diseases have tremendous psychological implications (67). Cushing's syndrome, hypothyroidism, and hyperprolactinemia/prolactinomas are found to be associated with anxiety and depression (67). Irreversible physical signs and symptoms persist despite prolonged cure of Cushing's disease and acromegaly, and can cause decreased perceived well-being (68;69). Furthermore, despite normalization of excessive endogenous hormone production or optimal hormone replacement strategies in hypopituitarism, persistent imperfections in endocrine homeostasis most likely result in subtle physiological and psychological derangements and impaired quality of life (70).

There is an increasing interest in the limbic-hypothalamic system and endocrine diseases (71). Assessment of functional and mental well-being has become an important outcome of long-term follow-up in pituitary adenomas. Quality of life refers to the perception of physical, mental, and social well-being of a person. Quality of life, measured with self-reported health parameters, is decreased in patients with pituitary adenomas (68;69;72-79). Several factors are related to this decreased well-being in pituitary adenomas: treatment modalities such as pituitary surgery or radiotherapy, and pituitary deficiencies (68;69;73;79). In prolactinomas, treatment with dopamine agonists and/or hyperprolactinemia can hypothetically induce irreversible neural changes that may affect quality of life (80).

In **chapter 4,** we assessed quality of life parameters in women treated for microprolactinomas. To assess whether there were differences in quality of life parameters between patients treated for different pituitary tumors, we compared quality of life parameters between large cohorts of patients with acromegaly, Cushing's disease, prolactinomas, and nonfunctioning macroadenomas in **chapter 5**.

8. Malignant prolactinoma

The incidence of pituitary carcinomas is extremely low (81). Until recently, only ~140 cases with pituitary carcinomas have been reported, one-third of them being malignant prolactinomas (82). Unless (distant) metastases have developed, it is very difficult to distinguish benign (invasive) prolactinomas from malignant prolactinomas. Overall, malignant prolactinomas present with atypical clinical symptoms, such as progressive symptoms of headache or cranial nerve

compression, and resistance to dopamine agonists, expressed by increasing prolactin levels. Furthermore, histological parameters such as proliferative Ki-67 index and p53 immunoreactivity are correlated with biological behaviour of pituitary adenomas (81;83). It is postulated that pituitary carcinomas arise from the transformation of initially large, but benign adenomas (81). This argument is based on observations that the initial presentation is not different from other macroadenomas, the long-duration needed for the transformation into carcinomas, and the increasing accumulation of genetic aberrations (83).

Once metastatic disease is established, treatment modalities are surgery, radiotherapy, and chemotherapy. In some patients, therapy with octreotide is an option. If tolerated, dopamine agonists should be continued. In **chapter 6**, we describe the remarkable history of a patient with a malignant prolactinoma, including a concise review of all cases reported in the literature with malignant prolactinomas.

OUTLINE OF THE PRESENT THESIS

Chapter 2: Evaluation of long-term outcome of patients with macroprolactinomas initially treated with dopamine agonists

Medical therapy with dopamine agonists is the treatment of choice in micro- and macroprolactinomas. Dopamine agonists have shown to be highly effective in reducing prolactin levels, restoring gonadal function, and inducing tumor shrinkage (11;12;14;15;17;19;20;30;31). Furthermore, remission after withdrawal of dopamine agonists depends on which dopamine agonist is used, and tumor shrinkage, but remission rates up to 64% are reported for macroprolactinomas. However, studies reporting the long-term clinical and radiological outcome after multimodality treatment in consecutive unselected patients are scarce (42;84-86). Furthermore, only one study reported pituitary deficiencies during long-term follow-up (84). Therefore, the aim of the study described in **chapter 2** was to assess long-term outcome in 72 consecutive patients with macroprolactinomas initially treated with dopamine agonists in our center.

Chapter 3: Evaluation of the prevalence of valvular heart disease in patients treated several years with dopamine agonists for prolactinomas

An increased risk of cardiac valve disease has been reported in patients with Parkinson's disease, treated with ergot-derived dopamine agonists, cabergoline or pergolide (57;58). The cardiac valve abnormalities, such as regurgitation and mitral valve thickening, manifest like myxoid degeneration, which resemble the valves obtained from patients with serotonin-secreting, carcinoid tumors, or from patients treated with anorectic drugs (dexfenfluramine, (nor) fenfluramine),or antimigraine ergot alkaloids drugs (ergotamine, methysergide) (87-92). The pathogenesis of these valvular abnormalities originates from the stimulation of the serotonin (5-HT_{2B}) receptors on cardiac valves by dopamine agonists. Stimulation of 5-HT_{2B}-receptors activates fibroblast mitogenesis, leading to valvular fibrosis and subsequent valvular dysfunction

(89;93). The question therefore arises whether there may also be a higher incidence of cardiac valve abnormalities in patients treated long-term with dopamine agonists for prolactinomas. Therefore, the aim of the study described in **chapter 3** was to assess the prevalence of valve regurgitation by tissue Doppler echocardiography in 78 patients treated long-term with ergot-derived or non-ergot derived dopamine agonists for prolactinomas.

Chapters 4 and 5: Assessments of quality of life parameters in patients treated for prolactinomas

Many patients with pituitary diseases suffer from decreased quality of life. Therefore, the assessment of quality of life has become of special interest in evaluating the ultimate outcome of the treatments of these pituitary tumors (68;69;72-79). Although prolactinomas often present with emotional disturbances, quality of life has not been assessed in patients with prolactinomas (80). Therefore, the aim of our study described in **chapter 4** was to assess quality of life parameters in patients treated for microprolactinomas. We chose to select patients with microprolactinomas for this study, since microprolactinomas do not suffer from other confounding effects of pituitary diseases, like hypopituitarism, other than secondary hypogonadism, mass effects of the tumor, or consequences of pituitary surgery or radiotherapy. We evaluated quality of life, using four validated, health-related questionnaires, in women with microprolactinomas, previously or currently treated with dopamine agonists, and compared them to controls subjects.

In clinical practice, the perception is that the treatment of different pituitary tumors is associated with slightly different outcomes with respect to parameters of quality of life. However, there are major differences in clinical characteristics of the different pituitary tumors, especially with respect to the distributions of gender and age. These are important factors in the evaluation of quality of life parameters, since increasing age and female gender are associated with worse scores of quality of life compared to younger patients and males. Therefore, the aim of the study described in **chapter 5** was to compare quality of life scores, adjusted for differences in age and gender distributions by standard deviation scores, of patients during long-term follow-up after treatment for different pituitary adenomas.

Chapter 6: Malignant prolactinoma

Malignant prolactinoma is a rare manifestation of prolactinomas. Clinical and biochemical parameters in these patients are of minimal utility to distinguish benign from malignant prolactinomas, and can mimic resistant, invasive prolactinomas. The diagnosis is in most of the cases established only at the moment metastasis occur. Adjuvant therapies are barely curative. The aim of the study described in **chapter 6** was to describe in detail the medical history of a female patient with malignant prolactinoma treated in our center, and to provide an overview of the clinical, biochemical, radiological, and histological characteristics and treatment modalities of all cases with malignant prolactinomas published in the literature.

Chapter 7: General discussion

In this chapter, the data obtained in the studies described in this thesis are put into perspective.

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Chapter 2

LONG-TERM OUTCOME OF PATIENTS WITH MACROPROLACTINOMAS INITIALLY TREATED WITH DOPAMINE AGONISTS

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ABSTRACT

Objective. Dopamine agonists are the first line therapy for the treatment of prolactinomas. The aim of this study was to assess long-term outcome of macroprolactinomas after initial treatment with dopamine agonists.

Design. Retrospective follow-up study.

Patients. We included 72 consecutive patients (age 39 ± 17 years, men 46%) diagnosed with macroprolactinoma, and initially treated with dopamine agonists between 1980 and 2004.

Results. Initial presentation included headache in 49%, and visual field defects in 38% of the patients. Median prolactin level at presentation of all patients was 428 µg/L (range 0.20–35398 µg/L). Hypopituitarism, other than hypogonadism, was present in 6% of the patients. Mean duration of follow-up was 10.2 ± 6.1 years. Additional transsphenoidal surgery was necessary in 35% of the patients, because of resistance and/or intolerance of dopamine agonists. Postoperative radiotherapy was provided to 18% of all patients. During long-term follow-up, normoprolactinemia was present in 85% of the patients, but biochemical remission (normal prolactin levels in the absence of dopamine agonists) was present in only 22% of the patients. Tumor shrinkage was evident on MRI in 57% of the patients. Hypopituitarism developed in 39% of the patients, especially in those who received additional surgery with or without radiotherapy.

Conclusion. Dopamine agonists are effective in restoring gonadal function, normalizing prolactin values, and inducing tumor shrinkage. However, in one-third of the patients, additional therapy was necessary due to dopamine agonist resistance and/or intolerance, associated with a high incidence of hypopituitarism.

INTRODUCTION

Prolactinomas are the most prevalent pituitary adenomas, accounting for 45-66% of all pituitary adenomas, with an estimated prevalence of 62 cases per 100.000 individuals (1;2). Macroprolactinomas (defined by a diameter > 1 cm) are present in only ~10% of the patients with a prolactinoma. Macroprolactinomas may present with visual field defects and headache due to mass effects of the tumor in both men and women, and with hyperprolactinemia related symptoms like amenorrhea and galactorrhea in premenopausal women (3). In some cases, macroprolactinomas are found as incidentalomas (4). The treatment of prolactinomas is aimed at reduction of tumor size, restoration of gonadal function, and, in the case of macroprolactinomas, also at improvement of visual field defects (5;6). Treatment with dopamine agonists is the first line of therapy for patients with macroprolactinomas. These drugs inhibit prolactin secretion and reduce tumor volume (5-10). However, in some patients intolerance due to nausea and postural hypotension, limit continuation of dopamine agonists, and additional treatment modalities, such as transsphenoidal surgery and/or radiotherapy, are necessary (11;12).

Many previous publications have documented the response to medical therapy (3;13-17). However, only few studies have addressed the long-term follow-up of macroprolactinomas initially treated with dopamine agonists, including endocrine and radiological outcome, and pituitary deficiencies (Table 1) (16;18-20). Those studies indicate that a considerable number of patients require subsequent surgical treatment, and in two of the studies additional post-operative radiotherapy was used (19;20). Nonetheless, there are remaining uncertainties with respect to the long-term outcome of patients treated for macroprolactinomas on remission and recurrence rates, and the effects of treatment on pituitary functions. Therefore, we assessed the long-term outcome of our patients with macroprolactinomas initially treated with dopamine agonists.

PATIENTS AND METHODS

Patients

Between 1980 and 2004, 72 consecutive patients visited the outpatient clinic of the Leiden University Medical Center for diagnosis and treatment of macroprolactinoma. Diagnostic criteria for macroprolactinoma included serum prolactin levels of at least four times above the upper limit of normal, and evidence of a pituitary macroadenoma of more than 10 mm in diameter on magnetic resonance imaging (MRI). Patients with macroprolactinemia, prolactin levels above the normal range secondary to primary hypothyroidism, or pituitary stalk compression, as well as patients using drugs known to increase prolactin levels, were excluded. In addition, we excluded one patient with a malignant prolactinoma, previously described in detail (21). All patients were assessed at presentation, and, subsequently, with intervals of 6 months during

Table 1. Long-term follow-up of macroprolactinomas initially treated with dopamine agonists

	Passos *et al.* (16)	Chattopadhyay *et al.* (18)	Berinder *et al.* (19)	Wu *et al.* (20)	Present study
Year of publication	2002	2005	2005	2006	2008
No. of patients	301*	29	21	14	72
M/F, *No.*	not reported	29/0	0/21	10/4	33/39
Age at diagnosis, *yr*	not reported	34	31†	32	39
Duration of follow-up, *yr*	not reported	2.6	9.1†	2.7	10.2
Treatment					
Dopamine agonist	brc	brc	brc/quin/cab	brc	brc/quin/cab
Surgery, %	22*	31	38	14	35
Radiotherapy, %	not reported	-	14	50	18
Outcome					
Hypopituitarism, %	not reported	55	not reported	not reported	39
Radiological recurrence, %	not reported	not reported	0†	0	4
Remission, %	8*	not reported	not reported	not reported	22

Data are expressed as mean, unless otherwise mentioned. Definition of hypopituitarism: pituitary deficiency of one or more axes. Definition of radiological recurrence: appearance of tumor mass without residual tumor mass on a previous MRI. Definition of remission: normal prolactin levels after withdrawal of dopamine agonist. M, male; F, female; yr, year; brc, bromocriptine; quin, quinagolide; cab, cabergoline.

* Micro- and macroprolactinomas

† Study of 271 women: 74 non-tumoral hyperprolactinemia, 160 micro-, and 21 macroprolactinomas (16 no initial imaging). Data: age at diagnosis and median duration of follow-up are of all (n=271) patients; follow-up radiological imaging is in n=8 patients with macroprolactinomas.

prolonged follow-up. Clinical characteristics, visual field reports, prolactin concentrations, other pituitary functions, and the size of the adenomas on sequential MRI images were assessed. The duration of follow-up in each patient was determined by the interval between the date of initial presentation and the date of the last visit to the outpatient clinic.

Growth hormone (GH) deficiency was defined by an insufficient rise in GH level (absolute value < 3 µg/L) after stimulation during an insulin tolerance test. At follow-up, premenopausal women were defined as LH/FSH deficient when amenorrhea was present, and postmenopausal women when gonadotropin levels were below the normal postmenopausal 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 at 08.00 h of less than 110 nmol/L and/or an insufficient rise in cortisol level (absolute value < 550 nmol/L) after stimulation by an insulin tolerance test or by CRH stimulation.

MRI

The pituitary tumors were assessed by MRI scanning. Tumor extension was classified as suprasellar, infra-/parasellar, or combined suprasellar and parasellar extension. According to the last MRI obtained during prolonged follow-up, the prolactinomas were classified as residual

tumor, tumor regrowth, recurrence, cystic degeneration, or no visible tumor. Tumor regrowth was defined as an increase in size of residual tumor. Recurrence was defined as appearance of tumor mass in a patient without residual tumor mass on a previous MRI.

Assays

Baseline prolactin levels were measured by an immuno-fluorometric assay using WHO-IRP 84/500, with an inter-assay variation coefficient of 3.4-6.2%, and intra-assay variation coefficient of 3.0-5.2%. The detection limit was 0.04 µg/L (Wallac Oy, Turku, Finland). Since 2004, prolactin levels were measured by an electrochemiluminescence immunoassay ("ECLIA") using Roche Elecsys 1010/2010 and Modular Analytics E170 (Elecsys module). The inter-assay variation coefficient was 2.3-3.1%, and the intra-assay variation coefficient was 1.8-1.9%. The detection limit was 0.47 µg/L (Roche, Basel, Switzerland). Normal values for random prolactin levels were less than 22 µg/L in men, and less than 30 µg/L in women, for both assays.

RESULTS

Clinical characteristics at presentation (Table 2)

Baseline clinical characteristics are reported in Table 2. The most prevalent presenting symptoms of macroprolactinomas, in both men and women, were headache (49%) and visual field defects (38%). In premenopausal women (n=30), amenorrhea was present in 73%, and galactorrhea in 67%.

At presentation, 9 patients were already treated with dopamine agonists, with a mean duration of 0.8 ± 0.9 year before presentation. Median prolactin level of the untreated patients was 460 µg/L (range 96–35398 µg/L). Pituitary deficiencies of one or more axes, other than hypogonadism, were present in only 6% of the patients, and none of the patients had panhypopituitarism.

MR imaging revealed a macroadenoma with infra-/parasellar extension in 26% of the patients, with suprasellar extension in 33% of the patients, and with both supra- and parasellar extension in 41% of the patients.

Treatment (Figure 1)

All patients were initially treated with either bromocriptine, quinagolide, terguride or cabergoline. Within one year of treatment, the presenting symptoms, headache and visual field defects, disappeared in 68% and 59% of the patients, respectively. Galactorrhea resolved in all female patients, and restoration of menses occurred in 64% of the premenopausal women within one year of therapy.

Table 2. Characteristics of patients with macroprolactinoma at presentation

Characteristic	*Value*
No. of patients	72
Mean age at diagnosis, *yr*	39 ± 17
Male, *%*	46
Clinical presentation, %	
Headache	49
Visual field defects	38
Amenorrhea	73
Galactorrhea	67
PRL at diagnosis[#], *μg/L*	428 (0.20–35398)
Hypopituitarism, %	
GH deficiency	-
LH/FSH deficiency	1
TSH deficiency	6
ACTH deficiency	4
Extension on imaging, %	
Infra-/parasellar	26
Suprasellar	33
Supra- and parasellar	41

GH, growth hormone; PRL, prolactin; yr, year. Prolactin: median, range in parentheses.

[#] Including 9 patients already on dopamine agonists at presentation.

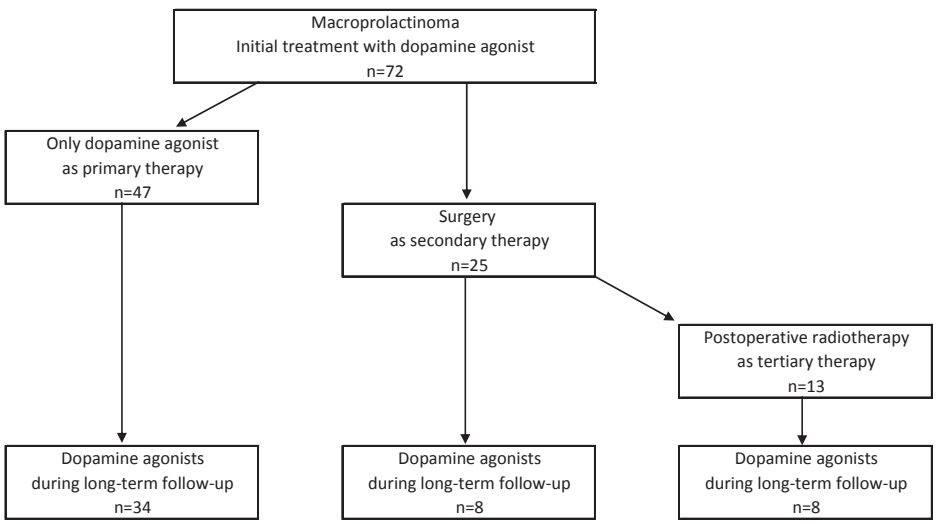

Figure 1

Treatment modalities in 72 patients with macroprolactinoma.

Intolerance to dopamine agonists

Overall, side effects were reported in 31 of the 72 patients (42%) treated with dopamine agonists. The most frequently reported symptoms included nausea (35%), headache, dizziness or vertigo (32%), fatigue (17%), orthostatic hypotension (3%), and psychiatric side effects (12%). Side effects were more frequently reported during the use of bromocriptine (39%, mean dose 8.4 mg/day), compared to quinagolide (25%, mean dose 0.139 mg/day), cabergoline (20%, mean dose 1 mg/week), or terguride (16%, mean dose 1.6 mg/day). Thirteen patients (18%) had to discontinue treatment because of intolerance for dopamine agonist therapy. Dopamine agonists used at the moment of interruption were: bromocriptine (n=7), quinagolide (n=4), cabergoline (n=1), or terguride (n=1). In 16 patients, treatment was switched to another dopamine agonist, and in 16 patients a dose reduction was required.

Additional treatment

Dopamine agonist treatment alone adequately treated macroprolactinoma and hyperprolactinemia in 47 of the 72 patients (65%). The remaining 25 patients (35% of total) needed additional treatment, after a mean duration of 1.2 years (range 0.3-8.5 years), by transsphenoidal surgery. Thirteen patients (18% of total) were treated by postoperative radiotherapy.

The surgically treated patients did not differ from the non-surgically treated patients with respect to the radiological characteristics, nor in the dopamine agonists used. Indications for surgery were resistance to dopamine agonists (n=20), resistance with intolerance to dopamine agonist therapy (n=3), rhinorrhea of cerebrospinal fluid (n=1), or meningitis (n=1). Although 12 of these 25 patients reported visual field defects at presentation, only 8 patients had persistent visual field defects prior to surgery. After surgery, visual fields improved in 7 of these 8 patients.

The mean interval between surgery and postoperative radiotherapy was 3.5 years (range 0.2-12.3 years). The indications for postoperative radiotherapy were the presence of a large residual tumor (n=9), tumor recurrence (n=2), and dopamine agonist resistance and intolerance (n=2). In 4 of these 13 patients, dopamine agonists had not been restarted after surgery because of serious intolerance. Median prolactin level before radiotherapy was 45 µg/L (range 3.4-1356 µg/L). The mean cumulative dose of radiotherapy was 44 Gy.

Long-term follow-up of all patients (Table 3, Figure 2)

Mean duration of follow-up of all patients was 10.2 ± 6.1 years.

Biochemical control and remission

Normal prolactin concentrations were present in 85% (61 of 72) of the patients. However, biochemical remission, *i.e.* normal prolactin levels without the use of any dopamine agonist, was present in only 16 of the 72 patients (22%). Eight of those patients had been treated with dopamine agonists only, and were in remission after withdrawal of dopamine agonist therapy

Table 3. Outcome of patients with macroprolactinoma during long-term follow-up

Outcome, No. (%)	**All**	**Only dopamine agonist**	**Additional surgery**	**Additional surgery and radiotherapy**
Patients	72	47	12	13
Biochemical outcome				
DA, normal prolactin	45 (63)	31	7	7
DA, elevated prolactin	5 (7)	3	1	1
Remission	16 (22)	8	4	4
No remission	5 (7)	4	-	1
Pregnant	1 (1)	1	-	-
Hypopituitarism				
GH deficiency	15 (21)	4	3	8
LH/FSH deficiency	14 (19)	5	5	4
TSH deficiency	17 (24)	3	6	8
ACTH deficiency	11 (15)	1	5	5
Radiological outcome				
Regrowth	5 (7)	4	-	1
Recurrence	3 (4)	-	1	2
Residual	18 (25)	9	4	5
Declining	25 (35)	25	-	-
No tumor visible	16 (22)	6	5	5
Cystic degeneration	4 (6)	2	2	-
Missing data	1 (1)	1	-	-

DA, dopamine agonist; GH, growth hormone.

(duration of treatment of 8.6 ± 8.3 years), with a follow-up duration after withdrawal of 4.4 ± 4.2 years. The other 8 patients with biochemical remission had been treated by additional transsphenoidal surgery (n=4) and postoperative radiotherapy (n=4).

Normal prolactin concentrations, but with continued dopamine agonist treatment, was present in 45 of the 72 patients (63%): 31 patients were treated with dopaminergic drugs only, 7 patients had been treated by additional transsphenoidal surgery, and 7 patients by transsphenoidal surgery followed by radiotherapy.

Persistent hyperprolactinemia was present in 15% of patients (n=11): in 8 patients treated with dopamine agonists only (one pregnant), in 1 patient after initial dopaminergic treatment followed by surgery, and in 2 patients after initial dopaminergic treatment followed by surgery and radiotherapy.

Hypopituitarism

For the whole cohort, hypopituitarism of one or more axes was present in 28 patients (39%), and panhypopituitarism in 3 patients (4%). Hypopituitarism of one or more axes, increased from 21% (10 of the 47 patients; no panhypopituitarism) treated with dopamine agonists only, to 67% (8 of the 12 patients; one patient with panhypopituitarism) treated with dopamine agonists

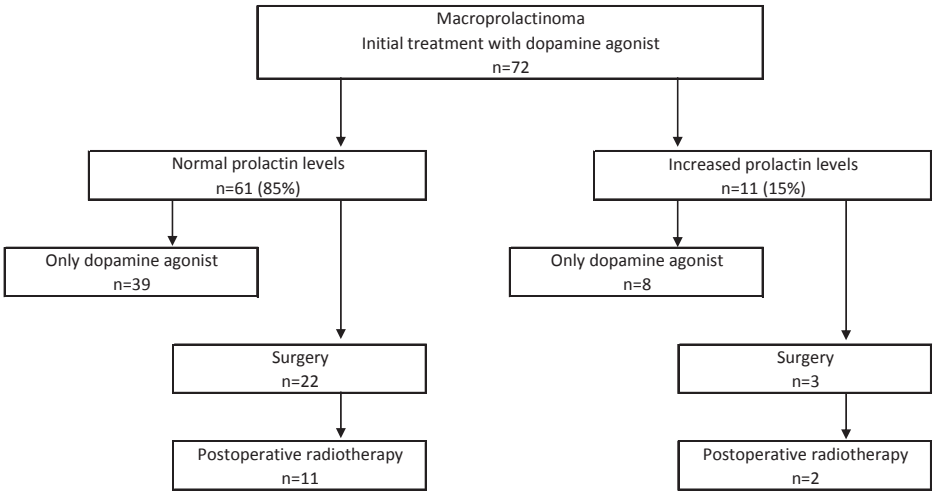

Figure 2

Outcome of prolactin levels in relation to treatment modalities during long-term follow-up of 72 patients with macroprolactinoma.

followed by transsphenoidal surgery, and to 77% (10 of the 13 patients; panhypopituitarism in 2 patients) after surgery followed by radiotherapy.

Radiological outcome

In 16 patients (22%), there was no visible tumor on MRI, whereas a reduction in adenoma size was noted in 25 patients (35%), and a residual adenoma in 18 patients (25%). In 5 patients (7%), there was regrowth of adenoma, whereas a recurrence was noted in 3 patients (4%). Cystic degeneration of the macroadenoma was reported in 4 patients (6%). In 10 patients a hemorrhagic zone developed within the macroadenoma during treatment (14%).

Mortality

At follow-up, 9 patients deceased (13%). The causes of death were not related to macroprolactinoma or its therapy. The data obtained during the last follow-up of these patients were used in the analyses.

DISCUSSION

We evaluated the long-term outcome of 72 consecutive men and women with macroprolactinomas treated initially with dopamine agonists. Additional treatment with transsphenoidal surgery was necessary in 35% of the patients, mostly for reason of drug resistance. In addition, postoperative radiotherapy was provided in 18% to treat recurrence or residual tumor. Although

control of hyperprolactinemia was achieved in 85% of cases, complete remission was present in only 22% of all patients during long-term follow-up. In the end, a considerable number of patients suffered from pituitary insufficiencies of one or more axes. These data indicate that macroprolactinomas require long-term dedicated care.

In general, this study supports the efficacy of dopamine agonists in the treatment of most patients with macroprolactinomas. Dopamine agonists are effective in restoring fertility, visual field defects, inducing normoprolactinemia and tumor shrinkage (8;22-24). Within one year of therapy, almost all presenting symptoms resolved in two-third of the patients, whereas tumor shrinkage occurred in 57% of the macroadenomas. Nevertheless, there are only limited studies reporting clinical, biochemical and radiological outcome during long-term follow-up of patients with macroprolactinomas initially treated with dopamine agonists (16;18-20). These studies, in combination with the current data, point to several characteristics of dopamine agonist treatment of macroprolactinomas, that should also be taken into account. Intolerance hinders continuation of dopamine agonists in some patients. In this retrospective follow-up study, dopamine agonist therapy was interrupted in 18% of the patients due to side effects. Moreover, in other patients resistance to dopamine agonists required additional treatment modalities, such as transsphenoidal surgery and radiotherapy. Therefore, the treatment of macroprolactinomas by dopamine agonists is not straight forward in a considerable number of the patients.

There are differences in efficacy and side effects between the different dopamine agonists. Bromocriptine normalizes prolactin levels, restores gonadal function, and induces tumor shrinkage in about 70% of the patients with macroprolactinoma (18;25;26). Disadvantages of bromocriptine treatment are the frequent occurrence of side effects and low remission rates after discontinuation (16;27). Tumor regrowth after discontinuation has been reported, although data on this issue are scarce (5). The non-ergot derived dopamine agonist quinagolide is also effective in normalisation of prolactin levels, fertility, and inducing tumor shrinkage, in 67-75% of the patients with macroprolactinomas, and is associated with less frequent side effects compared to bromocriptine (15;28-33). At present, cabergoline is the preferred dopamine agonist in the treatment of macroprolactinomas. Several studies have documented the efficacy of cabergoline in decreasing prolactin levels and tumor size, even in patients with resistance to other dopamine agonists (8;22;23;34;35). A large proportion of the patients in the present study were treated before the introduction of cabergoline in 1992 in the Netherlands. Therefore, the outcome may have been different if all patients had been initially treated with cabergoline. However, even cabergoline is associated with side effects, especially if high dosages are required in the treatment of complicated macroprolactinomas. Failure to achieve normal prolactin levels and/or a reduction of 50% in tumor size by dopamine agonists, *i.e.* resistance, is reported to occur in about one-third of the patients treated with bromocriptine, and in 10-20% of the patients treated with cabergoline (34;36). Alternative treatment options are to increase the dose of the dopamine agonist, to switch to another dopamine agonist, transsphenoidal

surgery, and postoperative radiotherapy. Approximately 79% of the patients resistant to both bromocriptine and quinagolide, do normalize their prolactin levels on cabergoline (35).

Surgery can be used as a second line treatment for macroprolactinomas. In our series, transsphenoidal surgery was considered necessary as a second line therapy in 32% of the patients because of resistance to dopamine agonists. In previous studies, surgery was used as a second line treatment in 14-38% of the patients (16;18-20). The remission rate in our study following additional surgery was 33%. Another study reported remission rate of 27% after surgery in 45 patients with macroprolactinomas, resistant to dopamine agonists (11). This low rate of remission contrasts with the success rates of surgery for macroadenomas in acromegaly (41%) and Cushing's disease (65%) in our center (37;38). Therefore, surgery is indicated for debulking, rather than for curing, of large macroprolactinomas in most patients.

Radiotherapy, indicated for residual tumor or tumor recurrence, was considered necessary in 44% of the patients after surgery. Wu *et al.* reported results of 14 patients with giant prolactinomas, treated with bromocriptine (20). Adjuvant radiotherapy was applied in 7 patients. At follow-up, prolactin levels were decreased in all patients, and normalized in only 3 patients. Eight patients presented with visual field defects, which improved in 3 patients. Tumor shrinkage occurred in all patients, with a reduction in volume of 61 to 100%. However, the effect of radiotherapy on pituitary function and remission rate are not reported. Literature data, including patients with therapy resistant prolactinomas, mostly after unsuccessful surgery, showed poor effects of radiotherapy in normalizing prolactin levels (overall only in ~34%) (5). Radiotherapy was mostly indicated for tumor mass control, rather than for treatment of hyperprolactinemia. Considering the potential side effects, especially hypopituitarism and increased incidence of intracranial malignancies, the use of radiotherapy should be carefully considered (39;40).

At presentation, macroprolactinomas are associated with a low incidence of pituitary deficiencies, other than suppressed gonadotropins. During long-term follow-up, hypopituitarism of one or more axes was present in 21% of the patients treated with dopamine agonists only, in 67% of the patients treated with dopamine agonists followed by transsphenoidal surgery, and in 77% of the patients who also received radiotherapy. Chattopadhyay *et al*. showed that surgery as a second line of treatment for macroprolactinomas was associated with hypopituitarism in 55% of the patients after mean follow-up of 2.6 years, in line with our observation (18). These disadvantages of surgical treatment, either with or without postoperative radiotherapy, of macroprolactinomas on pituitary function underscore dopamine agonists as the first line of treatment of macroprolactinomas.

We conducted a computer-based (PubMed) search of the literature to evaluate data on clinical outcome of macroprolactinoma initially treated with dopamine agonists. Articles were found, using the following inclusion criteria: macroprolactinoma, treatment with dopamine agonist, follow-up duration of more than 1 year. Articles with data using surgery and/or radiotherapy as primary treatment or inclusion criteria were excluded. Data concerning this subject are scarce, and only four articles were found (16;18-20). Furthermore, none of the articles reported

remission rates after prolonged follow-up, whereas two articles described data on radiotherapy. Prevalence of hypopituitarism after multimodality treatment was reported by one article, and radiological outcome in two studies, both with small number of patients (≤ 14).

This study evaluated the long-term biochemical and radiological outcome of multimodality treatment in patients with macroprolactinomas, initially treated with dopamine agonists. Medical therapy with dopamine agonists is the initial treatment of choice, with a long-term remission rate in only 22% of the patients. Additional transsphenoidal surgery was necessary in one-third of the patients, predominantly because of insufficient effective dopaminergic therapy or intolerance. Surgical treatment, alone or in combination with radiotherapy, resulted in remission rates in only one-third of these patients, with the expense of a considerable loss of pituitary functions. These data indicate that the treatment of macroprolactinomas requires long-term dedicated care.

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Chapter 3

AORTIC VALVE CALCIFICATION AND MILD TRICUSPID REGURGITATION, BUT NO CLINICAL HEART DISEASE AFTER 8 YEARS OF DOPAMINE AGONIST THERAPY FOR PROLACTINOMA

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J Clin Endocrinol Metab, in press

ABSTRACT

Objective. Treatment with ergot-derived dopamine agonists, pergolide and cabergoline, has been associated with an increased frequency of valvular heart disease in Parkinson's disease. The aim of the present study was to assess the prevalence of valvular heart disease in patients treated with dopamine agonists for prolactinomas.

Design. Cross-sectional study.

Patients. We performed two-dimensional and Doppler echocardiography in 78 consecutive patients with prolactinoma (mean age 47 ± 1.4 yr, 26% male, 31% macroprolactinoma) treated with dopamine agonists for at least 1 year (mean 8 ± 0.6 yr) and 78 control subjects. Patients were classified according to treatment: patients treated with cabergoline (group 1: n=47), and patients not treated with cabergoline (group 2: n=31).

Results. Clinically relevant valvular heart disease was present in 12% (9 of 78) of patients *vs*. 17% (13 of 78) of controls (P=0.141), and in 17% (8 of 47) of patients treated with cabergoline *vs*. 3% (1 of 31) of patients not treated with cabergoline (P=0.062). Mild tricuspid regurgitation was present in 41% of patients *vs*. 26% of controls (P=0.042), and aortic valve calcification was present in 40% of patients compared to 18% of controls (P=0.003). There was no relation between the cumulative dose of cabergoline and the presence of mild, moderate or severe valve regurgitation.

Conclusion. Several years of dopamine agonist treatment in patients with prolactinomas is associated with increased prevalence of aortic valve calcification and mild tricuspid regurgitation, but not with clinically relevant valvular heart disease. Therefore, additional studies on the adverse cardiac effects of dopaminergic drugs in prolactinoma are warranted, especially in patients with much longer use of these drugs.

INTRODUCTION

Long-term therapy with dopamine agonists is the treatment of choice for patients with prolactinomas, because of the high efficacy of these drugs in controlling hyperprolactinemia and tumor size. However, dopamine agonist therapy has been associated with valvular heart disease in patients with Parkinson's disease. Since 2002, several studies reported an association between treatment with pergolide, bromocriptine, or cabergoline and valvular heart disease (1-8). Recently, large population-based studies demonstrated an increased incidence and relative risk of developing cardiac valve disease in patients treated with pergolide or cabergoline for Parkinson's disease (9;10).

The cardiac abnormalities in these patients are manifested by fibrotic changes that cause thickening, retraction, and stiffening of valves. This may result in clinically significant regurgitation requiring valve replacement. However, these data from patients with Parkinson's disease can not be simply extrapolated to patients treated with dopamine agonists for prolactinomas, since gender and age of these patients, as well as duration and dosage of dopamine agonists, differ considerably from those used in patients with prolactinomas. Furthermore, it can not be excluded that disease-specific aspects are also involved. Hence, it is presently unclear whether the treatment of prolactinomas with dopamine agonists is also associated with valvular heart disease. Therefore, the aim of the present study was to assess the prevalence of valvular abnormalities in consecutive patients treated with dopamine agonists for prolactinomas.

PATIENTS AND METHODS

Patients and controls

In a cross-sectional study design, we included 78 consecutive patients with prolactinomas treated with dopamine agonists for at least one year. Diagnostic criteria for prolactinoma were serum prolactin levels at least two times above the upper limit of normal, and evidence of a pituitary tumor on computerized tomography scan or magnetic resonance imaging. A macroprolactinoma was defined by a diameter > 10 mm. Patients with macroprolactinemia, prolactin levels above the normal range secondary to primary hypothyroidism, or pituitary stalk compression, as well as subjects using drugs known to increase prolactin levels, were excluded. In addition, patients with concomitant growth hormone excess or -deficiency, or Parkinson's disease were excluded. None of the patients had myocardial infarction in the preceding five years, thyreotoxicosis, rheumatic fever, endocarditis, connective tissue disease, carcinoid syndrome, or used anorectic drugs. One female patient appeared to be pregnant (gestation duration of 14 weeks) at the moment of evaluation, and, as a consequence, was excluded.

Patients were divided into two study groups, according to dopamine agonist treatment. Group 1 consisted of patients treated with cabergoline (n=47). Group 2 consisted of patients

treated with bromocriptine, terguride, or quinagolide, or of patients who received other treatment modalities, such as surgery, without any dopamine agonists (n=31). All patients underwent a complete clinical and echocardiographic assessment.

We evaluated 78 control subjects matched for age, gender, body surface, and left ventricular systolic function, recruited from an echocardiographic database, as previously described (11). Exclusion criteria for these control subjects were the same as for the patients with prolactinoma. We controlled for left ventricular systolic function to avoid inclusion of patients with mitral regurgitation caused by left ventricular enlargement, with subsequent incomplete mitral leaflet closure. Those controls who were referred for echocardiographic evaluation of known valvular heart disease, murmur, congestive heart failure, or cardiac transplantation were also excluded. As a consequence, the control group comprised of subjects, who were referred for either atypical chest pain, palpitations or syncope without murmurs.

The study was performed because of the publications on the association between treatment with dopamine agonists and valvular disease. The Medical Ethics Committee of Leiden University Medical Center judged that this study was therefore part of regular patient care.

Anthropometric parameters

Height, weight, waist circumference, and blood pressure were measured at the outpatient clinic. Waist circumference was measured at the height of the umbilicus, using the same measuring-tape for all subjects. Normal values are < 102 cm for men, and < 88 cm for women. Blood pressure was measured automatically (Dinamap) six times during 20 minutes recording session. The lowest systolic and diastolic blood pressures were noted. Hypertension was defined as systolic pressure > 140 mmHg, or diastolic pressure > 90 mmHg, or the use of antihypertensive medication. All anthropometric parameters were measured by the same investigator.

Prolactin assay and normal values

Prolactin was measured using an electrochemiluminescence immunoassay ("ECLIA") using Roche Elecsys 1010/2010 and Modular Analytics E170 (Elecsys module), the inter-assay variation coefficient was 2.4-2.6%, the intra-assay variation coefficient was 1.8-1.9%. The detection limit was 0.047 µg/L (Roche, Basel, Switzerland). Normal values for basal PRL were < 15 µg/L in men, and < 23 µg/L in women.

Echocardiography, data acquisition

Echocardiography was performed with the subjects in the left lateral decubitus position using a commercially available system (Vingmed system Vivid-7; General Electric-Vingmed, Milwaukee, WI, USA). Standard 2-dimensional and color Doppler data, triggered to the QRS complex, were obtained using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal (long- and short-axis) and apical (2- and 4-chamber, long-axis) views. The images were stored for off-line analysis (EchoPac 6.0.1, General Electric Vingmed Ultrasound, Milwaukee, WI, USA). Left ventricular (LV)

dimensions were measured from M-mode images acquired from the parasternal long-axis view: inter-ventricular septum thickness (IVST), posterior wall thickness (PWT), LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), fractional shortening (FS), and LV ejection fraction (LVEF). Left ventricular mass (LVM) was calculated by the cube formula, and using the correction formula proposed by Devereux *et al*.: $0.8 \times (1.04\{[LVEDD + PWT + IVST]^3 - [LVEDD]^3\}) + 0.6$ (12).

The valvular assessment included the evaluation of morphology and function of the mitral, aortic and tricuspid valves. Color Doppler echocardiography was performed in all views after optimizing gain and Nyquist limit. Standard continuous-wave and pulsed-wave Doppler examinations were performed. Two independent expert readers blinded to clinical data performed the evaluation of regurgitated valve disease, using the semi quantitative and quantitative methods recommended by the American Society of Echocardiography (13). The severity of valvular regurgitation was determined on a qualitative scale according to the ACC/AHA guidelines for the management of patients with valvular heart disease: mild (grade 1), moderate (grade 2) and severe (grades 3-4) (14;15). Significant (clinically relevant) valvular heart disease was determined using the U.S. Food and Drug Administration (FDA) case definition: mild, moderate or severe aortic regurgitation, moderate or severe mitral regurgitation, or moderate or severe tricuspid regurgitation (16). Mild mitral regurgitation accompanied by prolapse, is also considered as significant valvular disease. In addition, the presence of leaflet or cusp abnormalities was evaluated. These abnormalities comprised the presence of local or widespread thickening, more than 5 mm, any calcification and motion abnormalities (restrictive or excessive). When tricuspid regurgitation was present, pulmonary artery pressure was estimated using the modified Bernoulli equation.

All echocardiograms were performed with the same equipment by single experienced independent observer, blinded for study groups. All data were analyzed by the sonographer and by another experienced independent observer, also blinded for study groups.

Statistical analysis

SPSS for Windows version 14.0 (SPSS, Inc., Chicago, IL, USA) was used to perform data analysis. Data were expressed as the mean ± SE, unless otherwise mentioned. The groups were compared with independent samples t-test or chi-square tests, when appropriate. Differences were considered statistically significant at $p < 0.05$. Prior to the study, we performed a sample size calculation, based on the only available data on valvular regurgitation in patients using cabergoline (10). Given the mean prevalence of any valvular regurgitation of 72% in patients with Parkinson's disease using cabergoline *vs*. 41% in controls, and, using a power of 90% and α at 0.05 (two sided), the estimated sample size was 42 subjects for each study group.

Table 1. Clinical characteristics of patients with prolactinomas and controls

Characteristic	**Prolactinoma n=78**	**Control Group n=78**	**P value**
Age, *yr*	47 ± 1.4	48 ± 0.9	0.318
Male sex, *No. (%)*	20 (26)	20 (26)	1.000
Body surface, m^2	1.9 ± 0.02	1.9 ± 0.02	0.314
Left ventricular measurements			
LVEDD, *mm*	50 ± 0.6	49 ± 0.7	0.366
LVESD, *mm*	28 ± 0.6	30 ± 1.0	0.195
IVST, *mm*	11 ± 0.3	10 ± 0.3	0.077
PWT, *mm*	10 ± 0.2	10 ± 0.2	0.506
LVM, *gram*	192 ± 8	174 ± 7	0.091
FS, *%*	43 ± 0.8	41 ± 0.8	0.054
LVEF, *%*	74 ± 1.1	71 ± 0.9	0.128

Data are expressed as mean ± SE, unless otherwise mentioned. The groups were compared with independent samples t-test or chi-square tests when appropriate. Yr, year; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; IVST, inter-ventricular septum thickness; PWT, posterior wall thickness; LVM, left ventricular mass; FS, fractional shortening; LVEF, left ventricular ejection fraction.

RESULTS

Clinical characteristics (Tables 1 and 2)

The clinical characteristics of the patients and controls are summarized in Table 1. The patients and controls did not differ with respect to age, gender and body surface area. In addition, left ventricular systolic function was normal in all patients and controls. At the moment of assessment, disease duration for all patients was 13 ± 0.7 years. A macroprolactinoma was present in 31% of the patients. Mean duration of dopamine agonist treatment was 8 ± 0.6 years (range 0-24.3 yr).

In the cabergoline treatment group (Group 1), disease duration was 12 ± 0.8 years. Duration of therapy with cabergoline was 5.2 ± 0.4 years (range 1-10.3 yr). The cumulative dose of cabergoline was 363 ± 55 mg (range 24 to 1768 mg) (Table 2).

In the other or no dopamine agonist treatment group (Group 2), disease duration was 14 ± 1.1 years. None of the patients had ever been treated with cabergoline.

Valvular regurgitation (Tables 3 and 4)

Significant valve regurgitation of any valve was present in 12% (9 of 78) of patients *vs*. 17% (13 of 78) of controls (P=0.141).

Mitral valve regurgitation was present in 28% (22 of 78) of patients *vs*. 23% (18 of 78) of controls (P=0.463). Significant regurgitation of the mitral valve (moderate or severe according to FDA criteria) was present in 3% (2 of 78) of patients *vs.* 1% (1 of 78) of controls (P=0.560).

Table 2. Clinical characteristics of patients treated for prolactinomas with cabergoline *versus* without cabergoline

Characteristic	**Cabergoline**		**P value**
	Yes n=47	**No n=31**	
Age, *yr*	46 ± 1.9	49 ± 2.3	0.361
Male sex, *No. (%)*	13 (28)	7 (23)	0.615
Body surface, m^2	1.9 ± 0.03	1.9 ± 0.03	0.388
Left ventricular measurements			
LVEDD, *mm*	50 ± 0.8	50 ± 1.0	0.828
LVESD, *mm*	28 ± 0.8	28 ± 1.0	0.924
IVST, *mm*	10 ± 0.4	11 ± 0.5	0.474
PWT, *mm*	10 ± 0.3	10 ± 0.4	0.958
LVM, *gram*	189 ± 10	195 ± 13	0.705
FS, *%*	43 ± 1.1	44 ± 1.3	0.591
LVEF, *%*	73 ± 1.5	74 ± 1.5	0.502
Years since diagnosis of prolactinoma, *yr*	12 ± 0.8	14 ± 1.1	0.112
Macroprolactinoma, *No. (%)*	15 (32)	9 (29)	0.797
Prolactin level at visit, *µg/L*	24 ± 4	28 ± 5	0.506
Number of patients, *No.*			
Cabergoline	47	-	
Bromocriptine	20	7	
Terguride	3	6	
Quinagolide	28	20	
No dopamine agonist	-	9	
Duration of therapy, *yr*			
Cabergoline	5.2 ± 0.4	-	
Bromocriptine	2.9 ± 0.9	3.9 ± 1.6	
Terguride	6.1 ± 3.0	2.0 ± 0.5	
Quinagolide	3.2 ± 0.5	8.9 ± 1.1	
Cumulative dose, *mg*			
Cabergoline	363 ± 55	-	
Bromocriptine	4216 ± 899	9779 ± 3679	
Terguride	2038 ± 645	903 ± 259	
Quinagolide	114 ± 18	395 ± 82	

Data are expressed as mean ± SE, unless otherwise mentioned. The groups were compared with independent samples t-test or chi-square tests when appropriate. Patients not treated with cabergoline, were treated with quinagolide, bromocriptine, terguride, or no dopamine agonist at all. Several patients, in both groups, had used more than one dopaminergic drug, although only one drug at a time. Yr, year; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; IVST, inter-ventricular septum thickness; PWT, posterior wall thickness; LVM, left ventricular mass; FS, fractional shortening; LVEF, left ventricular ejection fraction.

Aortic valve regurgitation was present in 6% (5 of 78) of patients *vs*. 13% (10 of 78) of controls (P=0.174). Mild aortic valve regurgitation was present in 4% (3 of 78) of patients *vs*. 13% (10 of 78) of controls (P=0.043). In patients treated with cabergoline, moderate aortic valve

Table 3. Valvular abnormalities in patients with prolactinomas and controls

Variable	**Prolactinoma n=78**	**Control Group n=78**	**P value**
Mitral valve			
Mitral regurgitation, *No. (%)*			
No MR	56 (72)	60 (77)	0.463
MR grade mild	20 (26)	17 (22)	0.572
MR grade moderate	2 (3)	1 (1)	0.560
MR grade severe	-	-	-
Mitral annulus, *mm*	32 ± 0.4	31 ± 0.5	0.557
Mean gradient, *mmHg*	1.2 ± 0.06	1.3 ± 0.06	0.188
Mitral area, cm^2	2.9 ± 0.06	3.1 ± 0.03	0.005
Mitral valve morphology, *No. (%)*			
Thickened leaflets	19 (24)	28 (36)	0.116
Calcifications	25 (32)	16 (21)	0.102
Leaflet motion abnormality	2 (3)	4 (5)	0.405
Aortic Valve			
Aortic regurgitation, *No. (%)*			
No AoR	73 (94)	68 (87)	0.174
AoR grade mild	3 (4)	10 (13)	0.043
AoR grade moderate	1 (1)	-	0.316
AoR grade severe	1 (1)	-	0.316
Aortic annulus, *mm*	20 ± 0.3	20 ± 0.2	0.237
Aortic sinus, *mm*	31 ± 0.5	31 ± 0.4	0.701
Sino-tubular junction, *mm*	23 ± 0.4	24 ± 0.4	0.095
Ascending aorta, *mm*	30 ± 0.6	29 ± 0.6	0.281
Aortic area, cm^2	2.4 ± 0.07	2.5 ± 0.07	0.174
Mean gradient, *mmHg*	4.0 ± 0.14	3.6 ± 0.15	0.057
Aortic valve morphology, *No. (%)*			
Bicuspid	2 (3)	1 (1)	0.560
Thickened leaflets	19 (24)	13 (17)	0.234
Calcifications	31 (40)	14 (18)	0.003
Leaflet motion abnormality	4 (5)	1 (1)	0.173
Tricuspid Valve			
Tricuspid regurgitation, *No. (%)*			
No TR	42 (54)	56 (72)	0.020
TR grade mild	32 (41)	20 (26)	0.042
TR grade moderate	4 (5)	2 (3)	0.405
TR grade severe	-	-	-
Pulmonary artery pressure, *mmHg*	29 ± 0.8	30 ± 1.3	0.474
Tricuspid valve morphology, *No. (%)*			
Thickened leaflets	3 (4)	-	0.080
Calcifications	2 (3)	-	0.155
Leaflet motion abnormality	1 (1)	1 (1)	1.000
Any significant valve regurgitation, *No. (%)*	9 (12)	13 (17)	0.141
Any thickened leaflets, *No. (%)*	30 (38)	31 (40)	0.870
Any calcifications, *No. (%)*	39 (50)	26 (33)	0.035

Data are expressed as mean ± SE, unless otherwise mentioned. The groups were compared with independent samples t-test or chi-square tests when appropriate. MR, mitral regurgitation; AoR, aortic regurgitation; TR, tricuspid regurgitation.

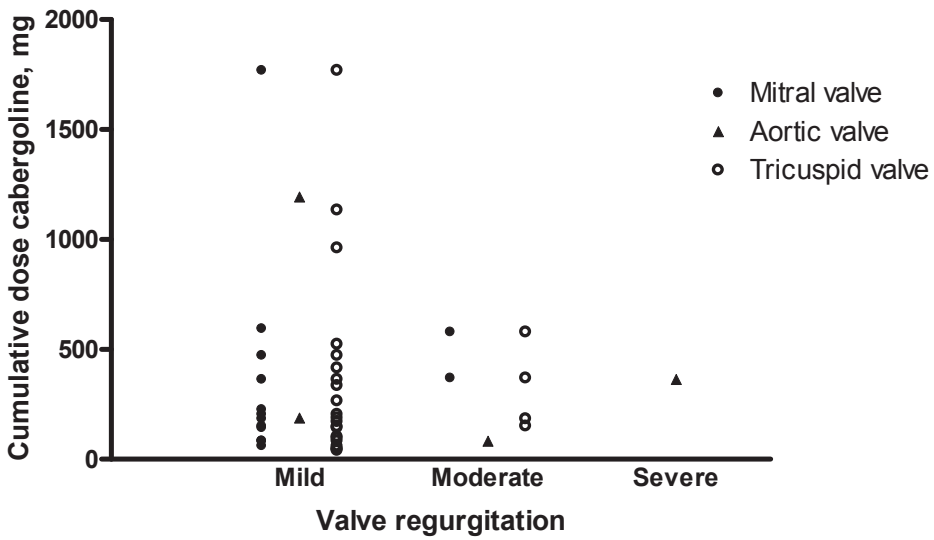

Figure 1.

There was no significant correlation between the cumulative dose of cabergoline and the presence of mild, moderate or severe valve regurgitation of the mitral, aortic and tricuspid valves in patients with prolactinomas.

regurgitation was present in one patient, and severe aortic valve regurgitation was present in another patient, but was absent in controls. One of these two patients appeared to have an asymptomatic, previously undiagnosed, congenital valvular abnormality (bicuspid aortic valve). Moderate or severe aortic regurgitation was absent in patients treated with other, or no dopamine agonist.

Mild, moderate or severe regurgitation of the tricuspid valve was present in 46% (36 of 78) of patients *vs.* 28% (22 of 78) of controls (P=0.020). Significant regurgitation of the tricuspid valve (moderate or severe according to FDA criteria) was present in 5% (4 of 78) of patients *vs.* 3% (2 of 78) of controls (P=0.405).

There was no relation between the cumulative dose of cabergoline and the presence of mild, moderate or severe valve regurgitation of the mitral, aortic and tricuspid valves in patients with prolactinomas (Fig. 1). Significant regurgitation of any valve was more frequent in the patients treated with cabergoline compared to the patients treated with other, or no dopamine agonist (P=0.062, Table 4). In patients treated with cabergoline, valvular regurgitation of one valve was present in 13% (6 of 47) of patients, valvular regurgitation of two valves in 4% (2 of 47) of patients, and none of the patients had valvular regurgitation of three valves.

Valvular morphology (Tables 3 and 4)

The prevalence of thickened leaflets and calcifications of the mitral valve was 24% (19 of 78) and 32% (25 of 78), respectively, in patients, and 36% (28 of 78) and 21% (16 of 78), respectively, in controls (P=0.116 and P=0.102, respectively).

Table 4. Valvular abnormalities in patients treated for prolactinomas with cabergoline *versus* without cabergoline

Variable	**Cabergoline**		**P value**
	Yes	**No**	
	n=47	**n=31**	
Mitral valve			
Mitral regurgitation, *No. (%)*			
No MR	33 (70)	23 (74)	0.702
MR grade mild	12 (26)	8 (26)	0.978
MR grade moderate	2 (4)	-	0.245
MR grade severe	-	-	-
Mitral annulus, *mm*	31 ± 0.6	32 ± 0.7	0.432
Mean gradient, *mmHg*	1.3 ± 0.08	1.1 ± 0.05	0.016
Mitral area, cm^2	2.9 ± 0.07	2.9 ± 0.11	0.790
Mitral valve morphology, *No. (%)*			
Thickened leaflets	15 (32)	4 (13)	0.056
Calcifications	18 (38)	7 (23)	0.146
Leaflet motion abnormality	2 (4)	-	0.245
Aortic Valve			
Aortic regurgitation, *No. (%)*			
No AoR	43 (92)	30 (97)	0.351
AoR grade mild	2 (4)	1 (3)	0.817
AoR grade moderate	1 (2)	-	0.414
AoR grade severe	1 (2)	-	0.414
Aortic annulus, *mm*	19 ± 0.4	20 ± 0.4	0.305
Aortic sinus, *mm*	31 ± 0.7	31 ± 0.7	0.525
Sino-tubular junction, *mm*	23 ± 0.6	23 ± 0.6	0.901
Ascending aorta, *mm*	30 ± 0.8	31 ± 0.7	0.361
Aortic area, cm^2	2.3 ± 0.10	2.5 ± 0.09	0.441
Mean gradient, *mmHg*	4.0 ± 0.17	4.1 ±0.25	0.735
Aortic valve morphology, *No. (%)*			
Bicuspid	2 (4)	-	0.245
Thickened leaflets	12 (26)	7 (23)	0.766
Calcifications	21 (45)	10 (32)	0.273
Leaflet motion abnormality	3 (6)	1 (3)	0.536
Tricuspid Valve			
Tricuspid regurgitation, *No. (%)*			
No TR	23 (49)	19 (61)	0.284
TR grade mild	20 (43)	12 (39)	0.736
TR grade moderate	4 (9)	-	0.095
TR grade severe	-	-	-
Pulmonary artery pressure, *mmHg*	29 ± 1.0	29 ± 1.3	0.636
Tricuspid valve morphology, *No. (%)*			
Thickened leaflets	3 (6)	-	0.151
Calcifications	1 (2)	1 (3)	0.764
Leaflet motion abnormality	1 (2)	-	0.414
Any significant valve regurgitation, *No. (%)*	8 (17)	1 (3)	0.062
Any thickened leaflets, *No. (%)*	22 (47)	8 (26)	0.062
Any calcifications, *No. (%)*	26 (55)	13 (42)	0.247

Data are expressed as mean ± SE, unless otherwise mentioned. The groups were compared with independent samples t-test or chi-square tests when appropriate. MR, mitral regurgitation; AoR, aortic regurgitation; TR, tricuspid regurgitation.

Thickened leaflets of the aortic valve were detectable in 24% (19 of 78) of patients, and in 17% (13 of 78) of controls (P=0.234). The prevalence of calcifications of the aortic valve was significantly higher in patients compared to controls (40% (31 of 78) *vs*. 18% (14 of 78), P=0.003).

Thickened leaflets and calcifications of the tricuspid valve were present in 4% (3 of 78) and 3% (2 of 78), respectively, of patients, compared to the absence of abnormalities of valve morphology in controls (P=0.080 and P=0.155, respectively).

The number of patients with thickening of the mitral leaflets was higher in the patients treated with cabergoline compared to the patients treated with other, or no dopamine agonist (P=0.056).

Subgroup analysis

Subgroup analysis of the patients treated with a cumulative dose of cabergoline of > 500 mg (n=11), showed significant valve regurgitation of two valves in one patient (cumulative dose 578 mg, duration of therapy 9.9 year), and significant valve regurgitation of one valve in another patient (cumulative dose 1193 mg, duration of therapy 3.3 year). Significant valvular regurgitation developed in one patient treated with quinagolide. The duration of therapy was 11.5 years, with a cumulative dose of 298 mg. Eight of the 9 patients with significant valve regurgitation were treated with cabergoline for mean period of 6.4 year (range 3.1-9.9 year), with a mean cumulative dose of 388 mg (range 82-1193 mg).

DISCUSSION

This study demonstrates that several years of treatment with dopamine agonists is associated with an increased prevalence of aortic valve calcification and mild tricuspid regurgitation in patients with prolactinomas. However, this treatment was not associated with an increased prevalence of clinically relevant valvular heart disease, even after the use of high cumulative doses of cabergoline up to 1768 mg. Nonetheless, we can not exclude the possibility that much longer treatment with dopamine agonists, than documented in the present study might result in clinically relevant changes in valvular function.

Dopamine agonists are used for several indications, such as Parkinson's disease, restless legs syndrome, and prolactinoma. In prolactinoma, dopamine agonist therapy is the treatment of choice. Dopamine agonists decrease prolactin levels, restore gonadal function, improve visual field defects and reduce tumor size. In contrast to patients with Parkinson's disease, patients treated for prolactinoma are predominantly young females, who are treated for at least 3-5 years with dopamine agonists. Cabergoline is the most potent dopamine agonist, and due to its favourable pharmacokinetic profile and well tolerance, is the most commonly used dopamine agonist in the treatment of prolactinoma. Recently, however, reports indicated an increased risk of developing valve regurgitation in patients with Parkinson's disease treated with the

ergot-derived dopamine agonists pergolide or cabergoline, with a mean cumulative dose cabergoline of 2820 gram for a mean duration of 2 years (9;10). As a consequence, questions regarding safety of medical treatment of prolactinoma patients with cabergoline emerged. Prospective trials, evaluating the effect of dopamine agonists on cardiac valves in patients with prolactinoma have not been published.

In this study, we compared echocardiographic data in patients with prolactinoma to control subjects derived from a database. Furthermore, patients treated with cabergoline were compared to patients treated with bromocriptine, terguride, or quinagolide, or no dopamine agonist therapy at all. Matched database analysis is necessary for several reasons. First, gender and age of patients with prolactinoma differ significantly from population based prevalence studies. Therefore, we individually matched each patient with prolactinoma for age, gender, body surface, and left ventricular systolic function to a control subject. Second, the influence of prolactin or prolactinoma on cardiac valves is unknown. Endocrine diseases, such as acromegaly and hypothyroidism, are associated with valvular regurgitation, cardiomyopathy, and congestive heart failure, but so far the influence of prolactin or prolactinoma on cardiac function and morphology has not been investigated (11;17-19). Therefore, in our study we compared the patients treated with cabergoline to patients treated with other, or no dopamine agonist, and compared them to control subjects.

A randomly selected control group without clinical indication for echocardiography would have been an optimal control group. However, controls from a database can also be used as representative controls (10;11). We recruited controls from a database, and excluded the control subjects referred for echocardiographic evaluation of known valvular heart disease, murmur, congestive heart failure, or cardiac transplantation. Other exclusion criteria were myocardial infarction in the preceding five years, thyreotoxicosis, rheumatic fever, endocarditis, connective tissue disease, carcinoid syndrome, or use of anorectic drugs. Moreover, the prevalence of valvular regurgitation in our controls was within the range reported in large population based studies (20). If selection bias of control subjects would nonetheless have occurred, this would have strengthened our conclusion, since this would have overestimated the prevalence of valvular disease in the controls, and consequently, underestimated the effects of dopaminergic drugs in patients with prolactinomas.

In general, the prevalence of clinically relevant mitral, aortic, or tricuspid valve regurgitation was not significantly higher in patients compared to controls. However, mild regurgitation of the tricuspid valve was significantly more prevalent in patients compared to controls (41% *vs*. 26%), whereas pulmonary artery pressures were not significantly different between these groups. The number of patients with thickening of the mitral leaflets was higher in patients treated with cabergoline compared to patients not treated with cabergoline (P=0.056, Table 4). In addition, significant regurgitation of any valve was more frequent in the patients treated with cabergoline compared to the patients not treated with cabergoline (P=0.062). Remarkably, we found an increased prevalence of calcifications of the aortic valve in patients treated with

cabergoline (45%) as well as in patients treated with other dopamine agonists or no dopamine agonist (32%), compared to control subjects (18%).

It is interesting to note, that by coincidence, two patients treated with cabergoline had bicuspid aortic valve. One of these 2 patients had severe aortic regurgitation, which was an indication for cardiac surgery. We observed that 8 of the 9 patients with significant valve regurgitation were treated with cabergoline for mean period of 6.4 year with a mean cumulative dose of 388 mg. Although, we found no relationship between the cumulative dose of cabergoline and severity of valvular regurgitation, the data do raise the question of whether a high cumulative dose of cabergoline is associated with valvulopathy.

On pathological examination, the cardiac valve abnormalities, such as regurgitation and mitral valve thickening, seen with ergot-derived dopamine agonists have the appearance of myxoid degeneration, which resemble the appearance of valves obtained from patients treated with anorectic drugs (dexfenfluramine, (nor)fenfluramine), antimigraine ergot alkaloids drugs (ergotamine, methysergide), and from patients with serotonin-secreting, carcinoid tumors (21-26). In accordance with those observations, stimulation of the serotoninergic system mediates the effects of dopamine agonists on cardiac valves. The ergot-derived dopamine agonists (cabergoline and pergolide) have binding affinity for D_2-receptors, as well as for serotonin (5-HT) receptors – in particular the 5-HT_{2B}-receptor, which are highly expressed on cardiac valves. Stimulation of 5-HT_{2B}-receptors activates fibroblast mitogenesis, leading to valvular fibrosis and subsequent valvular dysfunction (23;27). In contrast to bromocriptine and lisuride, which have a weak agonist activity, cabergoline and pergolide are potent agonists of 5-HT_{2B}-receptors, with high affinity for 5-HT_{2B}-receptors compared to bromocriptine (28).

The clinical relevance of calcifications of cardiac valves is unclear. Furthermore, the pathogenesis of these calcifications remains uncertain. Nonetheless, we can not exclude that this might be an early sign of the activation of the serotoninergic system on cardiac valves. It cannot be excluded either that hyperprolactinemia influences cardiac valve architecture. Therefore, additional studies are warranted, with a special focus on the pathological examination of the affected valves. Increased prevalence of significant tricuspid regurgitation associates with right sided related cardiac valve disease in the carcinoid syndrome, supporting a pathological substrate in the association between ergot-derived dopamine agonists and activation of the serotoninergic system on cardiac valves (25;29).

The current study does not confirm the associations previously observed in patients with Parkinson's disease between valvular regurgitation and treatment with the ergot-derived dopamine agonists pergolide or cabergoline. This may be related to differences in clinical characteristics between patients with Parkinson's disease and patients with prolactinomas. Patients with Parkinson's disease are much older than patients with prolactinomas. Moreover, there is a female preponderance in patients with prolactinomas. Finally, there are differences in the dosages of the dopamine agonists between the two diseases. In general, the dose of dopamine agonist treatment in Parkinson's disease is much higher than that used for treatment

of prolactinomas. For example, the mean daily dose of cabergoline in the study of Zanettini *et al.* was 3.6 mg, whereas patients treated with cabergoline for prolactinoma in the present study received a mean dose of 1.3 mg a week (9;10). We speculate that these discrepant factors are, at least in part, responsible for the discrepant associations between valvular heart disease and the use of dopamine agonists in these two conditions.

In conclusion, this study indicates that several years of treatment with dopamine agonists is associated with an increased prevalence of aortic valve calcification and mild tricuspid regurgitation in patients with prolactinomas. However, this treatment was not associated with an increased prevalence of clinically relevant valvular heart disease. These data indicate that additional studies on the adverse cardiac effects of dopaminergic drugs in prolactinoma are warranted, especially in patients with much longer use of these drugs, than documented in the present study.

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Chapter 4

QUALITY OF LIFE IS DECREASED IN FEMALE PATIENTS TREATED FOR MICROPROLACTINOMA

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Eur J Endocrinol 2007;157:133-139

ABSTRACT

Objective. Most studies on treatment of microprolactinoma have focused on clinical and biochemical outcome rather than on functional and mental well-being. We evaluated this topic in female patients with microprolactinoma, because other pituitary adenomas are associated with decreased quality of life.

Design. We conducted a cross-sectional study.

Patients and Methods. To assess the impact of treatment for microprolactinoma on subjective well-being, quality of life was investigated in 55 female patients (mean age 45 ± 10 years), treated for microprolactinoma in our center, using four validated, health-related questionnaires: Short-Form-36 (SF-36), Nottingham Health Profile (NHP), Multidimensional Fatigue Inventory (MFI-20), and Hospital Anxiety and Depression Scale (HADS). Patient outcomes were compared with those of 183 female controls with equal age distributions.

Results. Anxiety and depression scores were increased when compared with controls for all subscales as measured by HADS, and fatigue for all but one subscale as measured by MFI-20. Patients treated for microprolactinoma had worse scores on social functioning, role limitations due to physical problems (SF-36), energy, emotional reaction, and social isolation (NHP) when compared with control subjects. Important independent predictors of quality of life were reproductive status and anxiety and depression scores according to the HADS.

Conclusion. Quality of life is impaired in female patients treated for microprolactinoma, especially due to increased anxiety and depression. These increased anxious and depressive feelings might be due to possible effects of hyperprolactinemia on the central nervous system. Failure to recognize this association may adversely affect patient-doctor relationships.

INTRODUCTION

Prolactinomas, especially microprolactinomas, are the most prevalent pituitary adenomas (1-3). Dopamine agonist therapy is the treatment of choice for microprolactinoma (4). Up to 70% of patients with microprolactinoma treated with dopamine agonist therapy for several years may achieve long-term remission, evidenced by normoprolactinemia, following drug withdrawal (5;6).

Most studies on treatment of microprolactinoma have focused on biochemical outcome rather than functional recovery and well-being. However, other pituitary adenomas are associated with decreased quality of life (7). Quality of life is decreased in patients previously treated for acromegaly, Cushing's disease, and nonfunctioning pituitary macroadenomas (8-14). Moreover, exposure to excessive endogenous growth hormone or glucocorticoid concentrations in acromegaly and Cushing's disease, respectively, can cause irreversible signs and symptoms, which persist despite long-term cure of the disease (8;9). In patients previously treated for nonfunctioning pituitary macroadenomas, the presence of multiple pituitary deficiencies is a predominant predictor of decreased quality of life (10). Despite mimicry of endocrine homeostasis by optimal hormone replacement strategies, persistent imperfections in endocrine replacement therapies most likely result in subtle physiological derangements and impaired quality of life (15).

Evaluation of quality of life parameters in microprolactinoma will give more insight into the cause of the impaired quality of life in pituitary adenomas. Many factors that influence quality of life in other pituitary adenomas are absent in microprolactinomas, including mass effects of pituitary macroadenoma, hypopituitarism, the effects of surgery, and/or radiotherapy. However, most studies on quality of life in pituitary disease were not focused on prolactinoma. To our knowledge, only one study has been performed in prolactinoma patients. Johnson *et al*. found impairment in mental health measures in 39 patients with macro- or microprolactinomas when compared with a normal population, assessed by the Short-Form-36 (SF-36) questionnaire (7). Therefore, the purpose of the present study was to evaluate a broad spectre of physical, psychological, and social health aspects of quality of life in female patients treated for microprolactinoma. We assessed quality of life in female patients with microprolactinoma treated, previously or currently, in our center with dopamine agonists, using four validated, health-related quality of life questionnaires (SF-36, Nottingham Health Profile (NHP), Multidimensional Fatigue Inventory (MFI-20), and Hospital Anxiety and Depression Scale (HADS)). We compared the results with those of a control group with equal gender and age distributions.

PATIENTS AND METHODS

Protocol

To assess quality of life in patients treated for prolactinoma, we conducted a cross-sectional survey of all female patients treated with dopamine agonists for microprolactinoma in our department from 1980 to 2006. Diagnostic criteria for microprolactinoma were serum prolactin levels above 60 µg/L (two times upper boarder of normal value) and evidence of a pituitary tumor smaller than 10 mm in diameter on magnetic resonance imaging. Surgically treated patients and patients using drugs known to increase prolactin levels were excluded. Dopamine agonist therapy was started with 2.5 mg/day for bromocriptine, 0.5 mg/week for cabergoline, and 0.075 mg/day for quinagolide, and dose titration was based on clinical response and serum prolactin levels within the reference range. At the moment of assessment, all patients were visiting the outpatient clinic twice yearly. A total of 81 patients were asked to participate, and questionnaires were sent to their homes in prepaid envelopes. After six weeks, the patients who had not responded were sent a reminder letter and, thereafter, were contacted by telephone to encourage completion and return of the questionnaires. Each patient was also asked to provide a control person of comparable age and same gender (a relative, friend, or neighbour) to compose a control population with a comparable socio-economic status derived from the same geographical area. The control group was extended by controls derived from other studies in our center, who had been similarly approached (8-10;16;17).

In this study, gonadal axis was assessed by basal hormone measurements. In premenopausal women, hypogonadism was diagnosed by oligomenorrhea or amenorrhea and low gonadotropin levels. Other pituitary hormone levels were screened once yearly, none of the patients showed any pituitary hormone deficiencies, including growth hormone deficiency.

The study protocol was approved by the medical ethics committee of Leiden University Medical Center, and all subjects returning completed questionnaires gave written informed consent for participation in the study.

Questionnaires

Short-Form-36. The SF-36 questionnaire comprises 36 items and records general well-being during the previous 30 days (18;19). The items are formulated as statements or questions to assess eight health concepts: 1) limitations in physical activities because of health problems, 2) limitations in social activities because of physical or emotional problems, 3) limitations in usual role activities because of physical health problems, 4) bodily pain, 5) general mental health (psychological distress and well-being), 6) limitations in usual role activities because of emotional problems, 7) vitality (energy and fatigue), and 8) general health perceptions and change in health. Since the HADS and the MFI-20 (see below) are more specific questionnaires for mental health, the vitality and general mental health items were left out in this evaluation. Since the scores for the eight items are calculated separately from exclusive item-specific

questions (20), the results of the SF-36 items presented in this study are not influenced by the two items left out in this evaluation. Scores are expressed on a 0–100 scale, and higher scores are associated with a better quality of life.

Nottingham Health Profile. The NHP is frequently used in patients with pituitary disease to assess general well-being and consists of 38 yes/no questions, which are subdivided in six scales assessing impairments, *i.e.* pain (eight items), energy level (three items), sleep (five items), emotional reactions (nine items), social isolation (five items), and disability/functioning, *i.e.* physical mobility (eight items) (21;22). Subscale scores are calculated as a weight mean of the associated items and are expressed as a value between 0 and 100. The total score is the mean of the six subscales. A higher score is associated with a worse quality of life.

Multidimensional Fatigue Inventory. The MFI-20 comprises 20 statements to assess fatigue, which are measured on a five-point scale (23). Five different dimensions of fatigue (four items each) are calculated from these statements: 1) general fatigue, 2) physical fatigue, 3) reduced activity, 4) reduced motivation, and 5) mental fatigue. Scores vary from 0 to 20. Higher scores indicate greater experienced fatigue.

Hospital Anxiety and Depression Scale. The HADS consist of 14 items pertaining to anxiety and depression, which are measured on a four-point scale. Scores for the anxiety and depression subscale range from 0 to 21, and values for the total score range from 0 to 42. Higher scores indicate more severe anxiety or depression (24). A total score of 13 or more was considered increased.

Assays and normal values

Baseline prolactin levels were measured using an immunofluorometric assay using WHO-IRP 84/500, with an inter-assay variation coefficient of 3.4–6.2%, and detection limit of 0.04 µg/L (Wallac Oy, Turku, Finland). At the moment of assessment, prolactin was measured using an electrochemiluminescence immunoassay using Roche Elecsys 1010/2010 and Modular Analytics E170 (Elecsys module, Roche). The inter-assay variation coefficient was 2.3–3.1%, and the detection limit was 0.47 µg/L (Roche). Normal values for random prolactin levels were less than 30 µg/L in women for both assays.

Statistics

SPSS for Windows version 12.0 (SPSS Inc., Chicago, IL, USA) was used to perform data analysis. Data were expressed as the mean ± SD, unless otherwise mentioned. We used the independent samples t-test to compare quality of life outcomes between patients and controls. Independent variables affecting quality of life were explored with stepwise linear regression analysis. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Patients and controls

A total of 62 of the 81 patients (77%) responded to our survey. Seven of these patients preferred not to participate. Thus, 55 completed questionnaires (68%) were received.

The patient group consisted of 55 female patients, with a mean age of 45 ± 9.6 years. Patient characteristics are detailed in Table 1. There were no differences in clinical characteristics between the patients who returned and those who did not return the questionnaires.

Thirty-seven female controls were provided by the 55 patients who returned completed questionnaires. We extended these controls with 146 control persons of comparable age and same gender derived from other studies in our center, who had been similarly approached. Age was equally distributed among patients and controls, 45 ± 9.6 *vs*. 46 ± 9.7 years.

Clinical characteristics

All 55 patients had been treated with dopamine agonist therapy (bromocriptine, cabergoline, or quinagolide) for microprolactinoma. At the time of completion of the questionnaires, the mean disease duration was 14.4 years, 49% (n=27) of all the patients were still using dopamine

Table 1. Characteristics of 55 female patients treated for microprolactinoma

Characteristic	**Patients (n=55)**
Age, *yr*	45 ± 9.6
Pretreatment PRL level, *μg/L*	108.9 ± 120.8
Duration of disease, *yr*	14.4 ± 7.9
Duration of DA use, *yr*	9.3 ± 6.9
Present DA use (n=27)	11.8 ± 6.8
Previous DA use (n=28)	6.8 ± 6.2
Present DA use, *No. (%)*	27 (49)
Cabergoline	16
Quinagolide	9
Bromocriptine	2
Present PRL level, *μg/L*	31.9 ± 44.7
Present DA use	19.8 ± 19.8
Previous DA use	40.6 ± 35.8
Normoprolactinemia, *%*	67
Present DA use	76
Previous DA use	53
Reproductive status, *No. (%)*	
Premenopausal, regular menstrual cycle	19 (35)
Premenopausal, oral anticonceptives	5 (9)
Premenopausal, amenorrhoea	14 (25)
Postmenopausal	17 (31)

Data are given as mean ± SD, unless otherwise mentioned. DA, dopamine agonist; PRL, prolactin; yr, year.

agonists, and 76% of these patients had a normal prolactin value. Clinical remission, defined as normal prolactin value after withdrawal of dopamine agonists, was present in 53%. Sixty-nine percent (n=38) of all the women were premenopausal. Of these premenopausal women, 24 (63%) had regular menses at the time of completion of the questionnaires. Of the 55 patients, 18 had sought treatment for any psychiatric disorder (mainly depression) in the past. Three patients were still receiving medication for their psychiatric disorder: one patient used paroxetine, one fluoxetine, and one patient clozapine.

Quality of life in female patients with microprolactinoma compared with controls

Patients with microprolactinoma reported impaired quality of life when compared with the 183 control subjects (Table 2). The quality of life scores were significantly reduced in 12 out of 21 subscales when compared with controls (Fig.1).

Table 2. Summary of quality of life assessments in patients and controls

Questionnaire	**Patients (n=55)**	**Controls (n=183)**	**P value**
SF-36			
Physical functioning	85.5 ± 18.4	89.2 ± 16.0	NS
Social functioning	73.4 ± 28.6	87.0 ± 20.2	0.002
Role limitations due to physical problems	70.9 ± 38.1	74.3 ± 32.9	0.021
Role limitations due to emotional problems	75.8 ± 39.3	83.8 ± 33.9	NS
Bodily pain	81.2 ± 23.6	85.8 ± 19.6	NS
General health perception	67.6 ± 22.5	72.0 ± 19.4	NS
Change in health	50.9 ± 23.3	55.2 ± 17.6	NS
NHP			
Energy	19.1 ± 29.5	6.3 ± 20.0	0.005
Pain	6.6 ± 17.6	5.6 ± 16.6	NS
Emotional reaction	14.2 ± 24.0	5.6 ± 13.1	0.017
Sleep	11.0 ± 20.4	7.9 ± 19.0	NS
Physical ability	6.2 ± 13.3	3.4 ± 8.6	NS
Social isolation	11.3 ± 24.6	1.8 ± 7.4	0.007
MFI-20			
General fatigue	11.2 ± 5.4	8.5 ± 3.7	0.001
Physical fatigue	10.0 ± 4.9	7.4 ± 3.4	< 0.001
Reduced activity	8.3 ± 4.4	6.8 ± 3.1	0.020
Reduced motivation	8.8 ± 4.8	6.9 ± 3.1	0.006
Mental fatigue	8.9 ± 5.0	8.4 ± 4.0	NS
HADS			
Anxiety	6.1 ± 4.6	4.5 ± 3.2	0.022
Depression	4.4 ± 3.8	2.5 ± 2.8	0.001
Total	10.5 ± 7.8	7.1 ± 5.3	0.003

Data are given as mean ± SD, unless otherwise mentioned. Patients compared with controls by the independent samples t-test. NS, not significant.

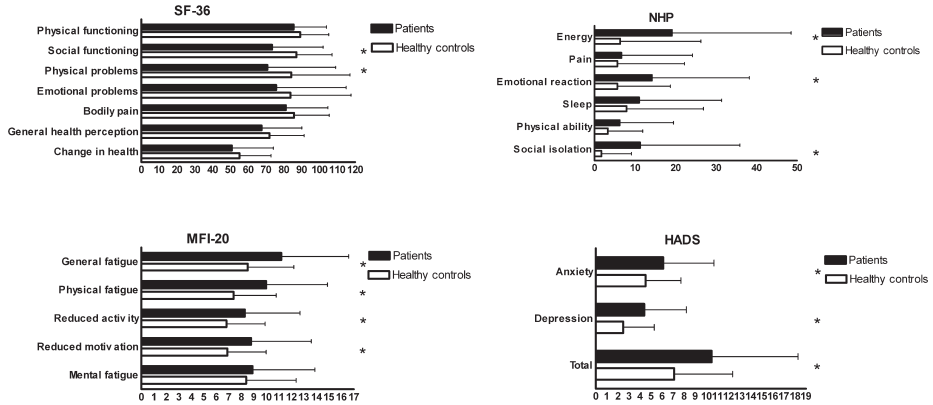

Figure 1.

Quality of life in female patients treated for microprolactinoma (n=55, black bars) and control subjects with the same age and gender distribution (n=183, white bars), according to SF-36, NHP, MFI-20, and HADS. Comparisons showing significant differences between patients and controls are shown by asterisks: * $p < 0.05$ patients *versus* controls.

In patients treated for microprolactinoma, the subscale for social functioning and role limitations due to physical problems of the SF-36, the energy, emotional reaction, and social isolation subscales of the NHP, and the general fatigue, physical fatigue, reduced activity, and reduced motivation subscales of the MFI-20 were impaired when compared with controls. Moreover, the patients also performed worse with respect to anxiety, depression and total scores for the HADS when compared with controls.

Factors affecting quality of life in female patients with microprolactinoma

No significant correlations were found between age and scores on the questionnaires in patients or in controls. The present use of dopamine agonists did not influence the scores on the questionnaires. There were no significant correlations between current prolactin concentrations and scores on questionnaires. There were no significant differences on scores of the questionnaires between patients with or without current hyperprolactinemia, or between patients with current hyperprolactinemia with or without present use of dopamine agonists. Analysis of premenopausal patients with or without hypogonadism revealed no significant differences on quality of life questionnaires scores.

Linear regression analysis

Linear regression analysis was performed in a model including age, present use of dopamine agonists, duration of dopamine agonist use, and reproductive status as independent variables and the questionnaire parameters as dependent variables to study factors determining quality of life in female patients with microprolactinoma. The increased scores on anxiety, depression and total anxiety and depression scales according to the HADS, in female patients treated for

microprolactinoma when compared with controls, could have influenced the other scores of the quality of life questionnaires. To assess this influence, the total anxiety/depression score of the HADS was also included in the linear regression model as independent variable and the other questionnaire parameters as dependent variables.

Duration of dopamine agonist use and age did not affect any of the scores in the regression model. Present use of dopamine agonist influenced the reduced activity scale of MFI-20. As shown in Table 3, anxiety and depression scores according to the HADS was a significant independent predictor of the other quality of life scales, independently of the other variables. Reproductive status also significantly influenced the scores of general fatigue, physical fatigue, reduced activity, reduced motivation scale (MFI-20), and of social functioning scale (SF-36).

Table 3. Linear regression analysis of factors determining quality of life in 55 female patients treated for microprolactinoma

Questionnaire	**Age (yr)**	**Present DA use (N/Y)**	**Duration of DA use (yr)**	**Reproductive status**	**HADS total score**
SF-36					
Physical functioning					-0.951 (0.004)
Social functioning				11.926 (0.014)	-2.226 (<0.001)
Role limitations due to physical problems					-2.375 (<0.001)
Role limitations due to emotional problems					-3.396 (<0.001)
Bodily pain					-1.149 (0.007)
General health perception					-1.675 (<0.001)
Change in health					
NHP					
Energy					2.210 (<0.001)
Pain					
Emotional reaction					2.384 (<0.001)
Sleep					
Physical ability					0.563 (<0.022)
Social isolation					2.195 (<0.001)
MFI-20					
General fatigue				-2.624 (0.055)	0.409 (0.050)
Physical fatigue				-2.275 (0.010)	0.395 (<0.001)
Reduced activity		-2.447 (0.027)		-2.083 (0.003)	0.406 (<0.001)
Reduced motivation				-1.846 (0.011)	0.414 (<0.001)
Mental fatigue					0.384 (<0.001)

Univariate stepwise regression analysis with the following parameters: age, present use of dopamine agonists, duration of dopamine agonist use, reproductive status, and total anxiety/depression score. Data are shown as the standardized β of independent predictive factors. P values are shown in parentheses. Reproductive status: premenopausal, regular menstrual cycle = 0; premenopausal, amenorrhoea = 1; postmenopausal = 2. DA, dopamine agonist; N, no; Y, yes; yr, year.

DISCUSSION

The results of the present study demonstrate that multiple aspects of quality of life are impaired in female patients with microprolactinoma after several years of treatment with dopamine agonists when compared with control subjects. These patients perceived reduced well-being, especially due to reduced motivation, fatigue, reduced emotional reaction, and more anxiety and depression. Current use of dopamine agonists appear to influence the results of quality of life on reduced activity, while the present prolactin levels did not affect the results at all. The data indicate subtle, persistent limitations in energy, and psychological and social functioning in patients, currently or previously, treated for microprolactinoma.

Most studies on treatment outcomes of prolactinoma have focused on clinical, biochemical, and tumor volume response rather than on functional and emotional well-being. To our knowledge, only Johnson *et al*. reported a systematic conducted study concerning quality of life in untreated patients with macro- or microprolactinomas, using the SF-36 questionnaire (7). In accordance with our results, their study showed reduced scores in role limitations due to physical and emotional problems, social functioning, vitality and mental health when compared with scores of the normal population. The present study, however, is the first cross-sectional study in microprolactinoma patients, evaluating various physical and psychological aspects after several years of treatment with dopamine agonists.

It may be argued that selection bias of patients and control subjects may have affected our data. Completed questionnaires were received of 68% of the patients. However, it seems unlikely that the non-responders have influenced the outcome of our data, because there were no differences in clinical characteristics between responders and non-responders.

This study indicates that patients, previously or currently, treated for microprolactinoma have decreased quality of life in line with results obtained in our center in patients with other pituitary diseases, including acromegaly, Cushing's disease, nonfunctioning pituitary macroadenoma, and craniopharyngioma (8-10;16). Strikingly, perceived well-being in patients treated for acromegaly is especially decreased due to physical limitations, whereas impaired quality of life in microprolactinoma patients is due to anxiety and depression. In patients with Cushing's disease and nonfunctioning pituitary macroadenoma, the quality of life is determined by fatigue and physical ability. Although quality of life is most severely impaired in patients during long-term follow-up after treatment for acromegaly (worse score on all 21 subscales of the four questionnaires when compared to own controls) (8) and Cushing's disease (worse score on 20 subscales of the same questionnaires when compared to own controls) (9), there might be disease-specific patterns in the long-term effects of pituitary diseases on quality of life parameters.

We used four health-related questionnaires to cover different dimensions of quality of life, including physical, emotional, mental and social aspects, which were validated for Western European subjects. These health-related questionnaires have not been developed to assess

quality of life specifically in patients with microprolactinoma, although the NHP and SF-36 are increasingly used in patients with pituitary disease (7;25). However, a disease-specific questionnaire such as developed for acromegaly (Acromegaly-Quality of Life) by Webb *et al*. is not available for prolactinoma (26). A disease-specific questionnaire for prolactinoma should also include questions related to gonadal and sexual function, as hyperprolactinemia results in secondary hypogonadism and negatively influences libido, mood and interest. In our study, 25% of the premenopausal women had amenorrhoea, denoting hypogonadism. It is likely that well-being is influenced by hypogonadism in these patients. It is difficult to assess whether hyperprolactinemia and/or hypogonadism cause(s) decreased quality of life in these female patients treated for microprolactinoma with dopamine agonists.

The interpretation of the underlying mechanisms of the association between pituitary adenoma and impaired quality of life is not completely answered. Unlike the patients studied in previous quality of life studies treated for acromegaly, Cushing's disease, or nonfunctioning macroadenoma, patients treated for microprolactinoma did not receive surgery and/or radiotherapy. In addition, they did not have pituitary deficiencies that could influence the quality of life parameters. The results of the regression analysis suggest a compromised quality of life due to the influence of anxiety and depression in these female patients treated for microprolactinoma. Despite withdrawal of dopamine agonists or normalization of prolactin levels, patients experience severe anxiety and depressive emotions, which can certainly influence experienced well-being. Treatment with dopamine agonists can elicit side-effects that could affect perceived well-being. However, neither the kind of dopamine agonist therapy, nor the present use of dopamine agonists, nor duration of dopamine agonist use showed to have influence on experienced well-being. Several points of view are possible to understand the relationship of prolactinoma and emotions, including the effects of hyperprolactinemia on the central nervous system, effects of hyperprolactinemia on peripheral tissues, and emotional changes associated with the knowledge of the presence of a pituitary tumor. There is an increasing interest in the interaction between the limbic-hypothalamic system and hormone release/action. In the pathophysiology of depression, the neurotransmitter serotonin is very important (27). There is evidence for a stimulatory role of serotonin in prolactin release in humans (27). Pharmacologic agents that increase synaptic availability (*e.g.* re-uptake inhibitors) of serotonin, used in the treatment of depression, have been found to increase prolactin concentrations. Conversely, the density and activity of dopamine receptors are modulated by prolactin and exerts an influence on dopamine transmission in the brain (28). The turnover of dopamine is inhibited by hyperprolactinemia in some central nervous structures and stimulated in others (28). Moreover, hyperprolactinemia has been documented to induce neural changes that may, ultimately, translate into changes in behavior, emotions and feelings (28). In addition to these putative effects of hyperprolactinemia, quality of life parameters may also be affected by the effects of dopamine agonist therapy on the brain. There are five dopamine receptors subtypes, each with specific neuroanatomical localization and function. Dopamine agonist for the D2

receptor, such as cabergoline, bromocriptine and quinagolide, are used to treat disorders such as Parkinson disease, drug abuse and restless legs (29). Dopamine D2 antagonist have been successfully applied in the treatment of schizophrenia, mania, and other psychiatric disorders. Therefore, it is possible that the impaired quality of life in patients with microprolactinoma is related to the effects of previous exposure to hyperprolactinemia and/or the effects of dopamine agonist therapy.

In conclusion, female patients treated for microprolactinoma have impaired self-reported quality of life due to emotional disturbances and fatigue with increased anxiety and depressive feelings. Therefore, treatment and follow-up should not only focus on the biochemical response and regain of menstrual cycle, but also on persistent psychological impairment. Failure to recognize this association between microprolactinoma and persistently impaired perceived well-being may adversely affect patient-doctor relationships (30).

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Chapter 5

DISEASE-SPECIFIC IMPAIRMENTS IN QUALITY OF LIFE DURING LONG-TERM FOLLOW-UP OF PATIENTS WITH DIFFERENT PITUITARY ADENOMAS

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Clin Endocrinol (Oxf), doi:10.1111/j.1365-2265.2008.03288

ABSTRACT

Objective. Quality of life (QoL) is impaired in patients treated for pituitary adenomas. However, differences in age and gender distributions hamper a proper comparison of QoL. Therefore, we compared age- and gender-specific standard deviations scores (Z-scores) of QoL parameters in patients treated for pituitary adenomas.

Patients and Methods. We determined Z-scores for health-related questionnaires (HADS, MFI-20, NHP, SF-36) in patients during long-term follow-up (13 ± 8 yrs) after treatment for pituitary adenomas. Z-scores were calculated by comparing the data of 403 patients (acromegaly (n=118), Cushing's disease (n=58), prolactinoma (n=128), nonfunctioning macroadenoma (n=99)) with a control population (n=440) for each subscales of the questionnaires and for total QoL score.

Results. All subscales of the questionnaires and the total QoL score were negatively affected in patients compared to controls. Comparing the Z-scores, patients treated for acromegaly reported more impairment in physical ability and functioning, and more bodily pain compared to patients treated for nonfunctioning macroadenoma and patients treated for prolactinoma. Patients with Cushing's disease reported impairment in physical functioning compared to patients treated for nonfunctioning macroadenoma. Linear regression analysis, with correction for age and gender, confirmed these findings. Additionally, Cushing's disease was associated with increased anxiety. Hypopituitarism negatively influenced multiple aspects of QoL.

Conclusion. QoL is impaired in patients during long-term follow-up after treatment of pituitary adenomas. Patients with pituitary adenomas should be informed on these persistent adverse effects of their disease on QoL to prevent inappropriate expectations with respect to the long-term results of treatment.

INTRODUCTION

Quality of life (QoL) is impaired during long-term follow-up of patients treated for pituitary adenomas (1-7). Different factors are related to this decrease in self-reported health-related parameters: radiotherapy (2;8;9), pituitary surgery (4), and pituitary deficiencies (10). In addition, there may be disease-specific effects of the different pituitary adenomas on QoL. This is supported by the only study, that compared QoL in patients with different pituitary adenomas by the questionnaires of the Short-Form-36 (SF-36) (11). In that study, patients with acromegaly had the greatest impairment in measures of physical function and patients with Cushing's disease had the most severe impairment in all measures of the SF-36 compared to patients with other pituitary adenomas (11).

There are major differences in age and gender distributions between the different pituitary adenomas. For instance, patients with Cushing's disease are predominantly female and are relatively young. In contrast, patients with a nonfunctioning pituitary macroadenoma have a more or less equal gender distribution and a higher mean age than patients with Cushing's disease. Because age and gender *per se* are major determinants of QoL (12-14), a proper comparison of QoL parameters between patients with different pituitary adenomas can only be performed after adjustment for these differences in age and gender distributions. This issue can be addressed by calculating age- and gender-specific standard deviation scores for each pituitary disease using a large group of healthy controls. Therefore, the aim of this study was to compare age- and gender-specific standard deviation scores of general health-related QoL questionnaires in patients during long-term follow-up after treatment for different pituitary adenomas to determine whether it is possible to identify disease-specific impairments of QoL. For this purpose, we assessed QoL in patients with acromegaly, Cushing's disease, prolactinoma, nonfunctioning pituitary macroadenoma, and in a large group of healthy controls.

PATIENTS AND METHODS

Patients

We included all consecutive patients visiting our out-patient clinic during long-term follow-up for acromegaly, Cushing's disease, prolactinoma and nonfunctioning macroadenoma. Primary study parameters were the results of the four health-related QoL questionnaires. Patients were asked to return questionnaires, which were sent to their home address in prepaid envelopes. After 6 weeks non-responders received a reminder letter, and, thereafter, they were contacted by telephone to encourage completion and return of the questionnaires.

Acromegaly: All patients previously treated for acromegaly who were now considered cured or biochemically well-controlled, based on recent biochemical evaluation were identified and sent QoL questionnaires (n=131) (8). The response rate was 90% (n=118). In patients without

treatment with somatostatin analogs cure of acromegaly was defined by a normal suppression of growth hormone (GH) levels (GH nadir <0.38 µg/L) during oral glucose loading and normal IGF-1 levels for age and gender. For conversion of GH concentration from µg/L to mU/L, multiply by 2.6. In patients with treatment of somatostatin analogs cure of acromegaly was defined by normal serum IGF-1 levels for age and gender and mean serum GH levels below 1.9 µg/L for all patients (obtained from 5 consecutive samples taken in the postabsorptive state with intervals of 30 min from 9.00 until 11.00 h a.m.). None of the patients was treated by Pegvisomant, at the time of the current study.

Cushing's disease: All patients previously treated for Cushing's disease who were considered cured on recent biochemical evaluation were identified and sent QoL questionnaires (n=63) (9). The response rate was 92% (n=58). Cure of Cushing's disease was defined by normal 24h urinary cortisol excretion rates (<220 nmol/24h) in two consecutive samples and by normal overnight suppression of plasma cortisol levels (<99.4 nmol/L) after 1 mg dexamethasone.

Prolactinoma: All patients treated for prolactinoma were identified and sent QoL questionnaires (n=190). The response rate was 67% (n=128). Criteria for prolactinoma were serum prolactin levels above 50 µg/L (1 µg/L = 36 mU/L) and evidence on MRI of a pituitary tumor without evidence of primary hypothyroidism or drugs that increase prolactin levels. To diagnose a macroprolactinoma, a tumor diameter on MRI of more than 1 cm and serum prolactin levels five times above reference values were required. Patients were treated with a combination of dopamine agonists, surgery or radiotherapy.

Nonfunctioning macroadenoma: All patients previously treated for nonfunctioning macroadenoma by transsphenoidal surgery were identified and sent questionnaires (n=128) (10). The response rate was 77% (n=99).

Controls: A control group was formed by healthy persons of comparable age and gender distribution from the direct social environment of the patients (8-10;15-17). The control group existed of 440 persons (138 men (31%), with a mean age of 51 years, range 17 to 89 years).

Paragangliomas: To compare the effects of pituitary adenomas on QoL parameters with another disease, we also included the assessment of a similar analysis in paraganglioma patients described in detail in a previous study (16). This group consisted of 82 patients (age 49 ± 12 yrs, 42 men) treated in our department because of paragangliomas.

The study protocol was approved by the medical ethics committee of the Leiden University Medical Center, and all subjects returning completed questionnaires gave written consent for participation in the study.

General follow-up of all patients

All patients were seen at least twice yearly by an endocrinologist, with appropriate evaluation and treatment of recurrent disease or of possible deficits of pituitary hormones. GH deficiency was defined as an IGF-1 level below the reference range for age and gender and/or an insufficient rise in GH levels (absolute value <3 µg/L) after stimulation during an insulin tolerance test

(glucose nadir <2.2 mmol/L). Prior studies have demonstrated that patients with multiple pituitary hormone deficiencies, including two or more pituitary hormone deficiencies other than GH deficiency, had a likelihood of approximately 95% of harboring GH deficiency (18-20). Based on these data, we classified patients, in whom GH-stimulation test data were not obtained, but who were deficient in 3 other pituitary axes, as GH deficient. When secondary amenorrhea was present for more than 1 year, premenopausal women were defined as LH/FSH deficient. 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 an insufficient increase in cortisol levels (absolute value <0.55 µmol/L) after a corticotrophin releasing hormone test or during an insulin tolerance test. If results were below the lower limit of the respective reference ranges, substitution with growth hormone, thyroxin, hydrocortisone or testosterone was started. In the case of amenorrhea and low estradiol levels in premenopausal women, estrogen replacement was provided.

Quality of life questionnaires

HADS (Hospital Anxiety and Depression Scale). The HADS consists of 14 items pertaining to anxiety and depression. Each item is measured on a 4-point scale. Scores for the anxiety and depression subscale range from 0-21 and for the total score from 0-42. A high score points to more severe anxiety and depression (21).

MFI-20 (Multidimensional Fatigue Inventory). The MFI-20 contains 20 statements to assess fatigue (22). Five different dimensions of fatigue (four items each) are calculated from these statements: 1) general fatigue, 2) physical fatigue, 3) reduced activity, 4) reduced motivation, and 5) mental fatigue. A higher score points to higher experienced fatigue.

NHP (Nottingham Health Profile). The NHP is frequently used in patients with pituitary disease to assess general well-being and QoL. The survey consists of 38 yes/no questions, which are subdivided in 6 scales assessing impairments, *i.e.* pain (8 items), energy level (3 items), sleep (5 items), emotional reactions (9 items), social isolation (5 items), and disability/functioning, *i.e.* physical mobility (8 items). A higher score is associated with more impairment (23;24).

SF-36 (Short-Form-36). The SF-36 questionnaire comprises 36 items and records general well-being during the previous 30 days. The items are formulated as statements or questions to assess eight health concepts: 1) physical functioning, 2) social functioning, 3) limitations in usual role activities because of physical health problems, 4) pain, 5) general mental health (psychological distress and well-being), 6) limitations in usual role activities because of emotional problems, 7) vitality (energy and fatigue), and 8) general health perceptions and change in health (25;26). Because the HADS and the MFI-20 are more specific questionnaires for mental health and fatigue, the vitality and general mental health items were left out in this evaluation. Higher scores are associated with better QoL.

Total QoL score. For an integral comparison of the QoL parameters addressed in the 4 questionnaires, we developed a total QoL score which is the sum of all different QoL questionnaire

subscales. First, all subscales of the questionnaires were converted to a 100-point score, in which a higher score is a worse quality of life. The SF-36 subscale scores were inverted. The HADS total score was not included, since this score is obtained by simply adding the HADS anxiety and depression scores. Subsequently, all 20 subscale scores were added and divided by 20, generating a total QoL score (minimal value 0, maximal value 100). Therefore, a higher score indicates a greater impairment of QoL.

Statistics

Statistical analysis was performed using SPSS for Windows, version 12.0 (SPSS Inc. Chicago, Illinois, USA). Results are expressed as the mean ± SD or mean with 95% CI, unless specified otherwise. Normal distribution of data was verified by the Kolmogorov-Smirnov test.

Calculation of Z-scores: Gender-specific mean and standard deviation values could be calculated per decade of age, because all QoL data obtained in the healthy controls were approximately normally distributed. Using these values, age- and gender-specific Z-scores could be calculated for each individual patient in the different groups of pituitary adenomas. The Z-score reveals how many units of the standard deviation a case is above or below the mean. The Z-score is calculated by the following formula: $Z=(x-\mu)/\sigma$, where x=individual QoL value, μ=mean QoL value of controls of equal gender and age, and σ=standard deviation of QoL value of controls of equal gender and age. The Z-score could be calculated for all subscales of the four different questionnaires (21 subscales) and the total QoL score. Since a higher score is a worse QoL at the HADS, MFI-20, NHP, and the total QoL score, a positive Z-score denotes a decreased QoL compared to healthy controls. In contrast, in the SF-36 scales a higher score reflects a better QoL and, consequently, negative Z-scores in the SF-36 denote a decreased QoL compared to healthy controls.

Hypothesis testing: First, absolute QoL scores were compared between all patients with pituitary adenomas and controls by independent samples t-tests. Subsequently, the Z-scores of each QoL score were compared between the patients groups with the different pituitary adenomas by analysis of variance with post-hoc comparisons with Tukey's HSD correction for multiple comparisons. Finally, linear regression analysis was performed in a model using the absolute scores of questionnaire subscales and total QoL score as dependent variables and age, gender, patient group, radiotherapy, follow-up duration, and hypopituitarism as independent variables. A p-value of <0.05 was considered to be significant.

RESULTS

Clinical characteristics of the patients (Table 1)

Acromegaly: The mean age of the patients with acromegaly (61 men) was 59 ± 13 years. Treatment for acromegaly consisted of transsphenoidal surgery in 92%, radiotherapy in 28%

Table 1. Clinical characteristics of the 403 patients with pituitary adenomas

Characteristic		**Acromegaly (n=118)**	**Cushing's disease (n=58)**	**Prolactinoma (n=128)**	**Nonfunctioning macroadenoma (n=99)**
Age, *yr*		58.6 ± 12.9	51.7 ± 15.2	48.3 ± 12.7	61.9 ± 11.7
Follow-up duration, *yr*		12.0 ± 7.4	13.4 ± 6.7	15.1 ± 8.7	9.9 ± 6.6
Gender, *No. (%)*	Men	61 (52)	10 (17)	29 (23)	54 (55)
	Women	57 (48)	48 (83)	99 (77)	45 (45)
Surgery, *No. (%)*		108 (92)	58 (100)	34 (27)	99 (100)
Radiotherapy, *No. (%)*		33 (28)	11 (19)	13 (10)	37 (37)
ACTH deficiency, *No. (%)*		30 (25)	28 (48)	15 (12)	61 (63)
TSH deficiency, *No. (%)*		28 (24)	21 (36)	28 (22)	59 (62)
GH deficiency, *No. (%)*		2 (2)	13 (22)	9 (7)	81 (83)
LH/FSH deficiency, *No. (%)*	Men, *No. (% of men)*	16 (26)	1 (10)	10 (35)	43 (80)
	Premenopausal women, *No. (% of premenopausal women)*	4 (14)	7 (25)	3 (4)	8 (80)
ADH deficiency, *No. (%)*		4 (4)	11 (19)	3 (2)	9 (9)

Data are presented as mean ± SD or as number (percentage). GH, growth hormone; yr, year.

(postoperative treatment in 31 patients and primary treatment in 2 patients), somatostatin analog therapy in 22% of the patients (postoperative treatment in 17 patients and primary treatment in 7 patients). At the time of evaluation, 22% of the patients were using somatostatin analogs. The duration of cure of biochemical control of the disease at the time of evaluation was 12 ± 7 years.

Cushing's disease: The mean age of the patients with Cushing's disease (10 men) was 52 ± 15 years. Treatment for Cushing's disease consisted of transsphenoidal surgery in all patients, additional radiotherapy in 19%, and additional bilateral adrenalectomy in 5% of the patients. The duration of remission at the time of evaluation was 13 ± 7 years.

Prolactinoma: The mean age of the patients with prolactinoma (29 men) was 48 ± 13 years. Sixty-nine percent of women and 24% of men had a microadenoma (total n=75). Treatment of the prolactinoma consisted of primary dopamine agonist drug therapy in 84%, additional surgery in 11% of patients, radiotherapy in 6% of patients, primary surgery in 12% or a combination of surgery and radiotherapy in 4% of patients. Fifty-eight patients (45%) used dopamine agonist drugs at the time of evaluation. Mean prolactin concentrations were 21.2 ± 39.8 µg/L in those patients compared to 40.9 ± 51.4 µg/L in those without dopamine agonist drugs. At the time of the assessment of quality of life parameters, mean prolactin concentrations were 37.8 ± 46.5 µg/L in patients with microprolactinoma, and 19.1 ± 44.4 µg/L in patients with macroadenoma. The mean follow-up period after initial diagnosis was 15 ± 9 years.

Nonfunctioning macroadenoma: The mean age of the patients with nonfunctioning macroadenoma (54 men) was 62 ± 12 years. All patients were treated primarily by transsphenoidal surgery. Twenty-two patients had received prophylactic postoperative radiotherapy (22%).

Table 2. Absolute QoL scores of patients with pituitary adenomas and healthy controls

Questionnaire	**Patients (n=403)**	**Healthy controls (n=440)**	**P value**
Total QoL score	31.1 ± 18.0	20.2 ± 11.7	<0.001
SF-36			
Physical functioning	75.2 ± 26.1	88.2 ± 16.6	<0.001
Social functioning	76.4 ± 26.0	88.3 ± 18.8	<0.001
Role limitations due to physical problems	62.1 ± 41.7	84.3 ± 31.3	<0.001
Role limitations due to emotional problems	70.0 ± 40.7	86.5 ± 29.5	<0.001
Bodily pain	76.7± 24.0	85.7 ± 18.6	<0.001
General health perception	57.9 ± 24.1	71.6 ± 18.7	<0.001
Change in health	49.6 ± 22.0	53.6 ± 17.9	0.004
NHP			
Energy	29.2 ± 38.4	6.2 ± 18.7	<0.001
Pain	12.6 ± 23.7	4.9 ± 14.6	<0.001
Emotional reaction	15.5± 23.9	5.5 ± 13.7	<0.001
Sleep	17.4 ± 26.9	8.9 ± 19.2	<0.001
Physical ability	13.5 ± 22.2	4.0 ± 10.3	<0.001
Social isolation	10.2 ± 21.6	2.4 ± 8.5	<0.001
MFI-20			
General fatigue	11.8 ± 5.3	8.5 ± 4.0	<0.001
Physical fatigue	11.1 ± 5.0	7.6 ± 3.7	<0.001
Reduced activity	10.1 ± 4.9	7.2 ± 3.4	<0.001
Reduced motivation	9.5 ± 4.7	7.3 ± 3.4	<0.001
Mental fatigue	10.0 ± 5.1	7.8 ± 3.9	<0.001
HADS			
Anxiety	5.7 ± 4.2	4.0 ± 3.2	<0.001
Depression	4.8 ± 4.4	2.8 ± 2.9	<0.001
Total	10.5 ± 7.8	6.8 ± 5.3	<0.001

Data are expressed as mean ± SD, and compared by independent samples t-test.

Tumor recurrence was treated by radiotherapy in 11 patients (11%) and combined surgery and radiotherapy in 4 (4%). The mean follow-up period after primary treatment was 10 ± 7 years.

Comparison of absolute QoL scores between patients with pituitary adenomas and healthy controls (Table 2)

We compared the results of the questionnaires from 403 patients with pituitary adenomas (154 men (38%), mean age of 55 years, range 22 to 89 years) with those obtained from 440 control subjects (138 men (31%), mean age of 51 years, range 17 to 89 years). All subscales of the HADS, MFI-20, SF-36, and NHP were negatively affected in the patients compared to the controls. Total QoL score was significantly higher compared to the healthy controls, indicative for an impaired QoL in patients with pituitary adenomas.

Comparison of Z-scores between patient groups with different pituitary adenomas (Table 3)

Perceived quality of life is significantly different between the patient groups (P=0.003) assessed by the total QoL Z-score, and is especially decreased in patients treated for acromegaly compared to patients treated for nonfunctioning macroadenoma (P=0.006) and to patients treated for prolactinoma (P=0.011).

There were no disease-specific differences in the Z-scores for the subscales of the HADS and MFI-20. The Z-scores for energy, pain, emotional reaction, sleep, and social isolation according to the NHP did not differ between the patient groups. The Z-scores for physical ability, however, did differ significantly between the patient groups (P=0.002). Patients previously treated for

Table 3. Z-scores (mean, 95% CI) of QoL in patients treated for acromegaly, Cushing's disease, prolactinoma, and nonfunctioning macroadenoma

Questionnaire	**Acromegaly (n=118)**	**Cushing's disease (n=58)**	**Prolactinoma (n=128)**	**Nonfunctioning macroadenoma (n=99)**	**ANOVA P value**
Total QoL score	1.4 (1.0, 1.7)	1.1 (0.6, 1.5)	0.7 (0.4, 1.0)	0.5 (0.1, 0.9)	0.003
SF-36					
Physical functioning	-1.4 (-1.8, -0.6)	-1.3 (-1.9, -0.6)	-0.7 (-1.0, -0.3)	-0.3 (-0.7, -0.02)	0.001
Social functioning	-0.6 (-0.8, -0.3)	-0.8 (-1.2, -0.3)	-0.8 (-1.1, -0.5)	-0.6 (-0.9, -0.3)	0.677
Role limitations due to physical problems	-1.0 (-1.3, -0.7)	-0.7 (-1.1, -0.2)	-0.8 (-1.0, -0.5)	-0.7 (-1.1, -0.4)	0.333
Role limitations due to emotional problems	-0.9 (-1.3, -0.7)	-0.6 (-1.0, -0.2)	-0.5 (-0.8, -0.2)	-0.8 (-1.2, -0.4)	0.454
Bodily pain	-0.8 (-1.0, -0.5)	-0.6 (-1.0, -0.2)	-0.4 (-0.7, -0.2)	-0.2 (-0.4, 0.04)	0.015
General health perception	-0.8 (-1.1, -0.6)	-0.9 (-1.2, -0.5)	-0.6 (-0.9, -0.3)	-0.6 (-1.0, -0.3)	0.536
Change in health	-0.2 (-0.4, 0.04)	-0.1 (-0.4, 0.3)	-0.3 (-0.5, -0.1)	-0.04 (-0.3, 0.2)	0.392
NHP					
Energy	1.3 (0.9, 1.7)	1.3 (0.7, 1.8)	1.2 (0.4, 1.4)	1.2 (0.6, 1.7)	0.982
Pain	1.4 (0.6, 2.1)	1.2 (-0.005, 2.5)	0.4 (-0.04, 0.8)	1.0 (-0.2, 2.1)	0.255
Emotional reaction	1.5 (0.3, 2.7)	0.9 (0.4, 1.5)	0.6 (0.2, 1.0)	1.5 (0.4, 2.5)	0.398
Sleep	0.8 (0.5, 1.2)	0.4 (0.03, 0.9)	0.4 (0.1, 0.7)	0.8 (0.3, 1.3)	0.249
Physical ability	1.6 (1.0, 2.1)	1.1 (0.5, 1.8)	0.6 (0.2, 0.9)	0.4 (0.04, 0.8)	0.002
Social isolation	1.1 (0.4, 1.7)	1.1 (0.2, 1.9)	0.9 (0.4, 1.4)	1.4 (0.5, 2.3)	0.677
MFI-20					
General fatigue	1.1 (0.9, 1.4)	0.9 (0.5, 1.2)	0.7 (0.4, 1.0)	0.8 (0.5, 1.2)	0.279
Physical fatigue	1.1 (0.8, 1.4)	1.0 (0.7, 1.4)	0.9 (0.6, 1.2)	0.7 (0.4, 1.0)	0.290
Reduced activity	0.9 (0.7, 1.2)	0.8 (0.4, 1.2)	0.8 (0.5, 1.0)	0.8 (0.5, 1.2)	0.830
Reduced motivation	0.7 (0.5, 1.0)	0.7 (0.3, 1.1)	0.5 (0.3, 0.8)	0.7 (0.3, 1.0)	0.717
Mental fatigue	0.6 (0.4, 0.9)	0.9 (0.5, 1.3)	0.5 (0.2, 0.7)	0.6 (0.3, 0.9)	0.383
HADS					
Anxiety	0.7 (0.4, 0.9)	0.7 (0.3, 1.1)	0.5 (0.2, 0.7)	0.5 (0.2, 0.8)	0.626
Depression	0.8 (0.5, 1.1)	0.7 (0.3, 1.1)	0.7 (0.4, 1.0)	0.6 (0.2, 1.0)	0.745
Total	0.9 (0.5, 1.2)	0.8 (0.4, 1.3)	0.6 (0.3, 0.9)	0.6 (0.2, 0.9)	0.692

Data of the 4 different groups were compared by analysis of variance. The overall p-value of this comparison between groups is provided.

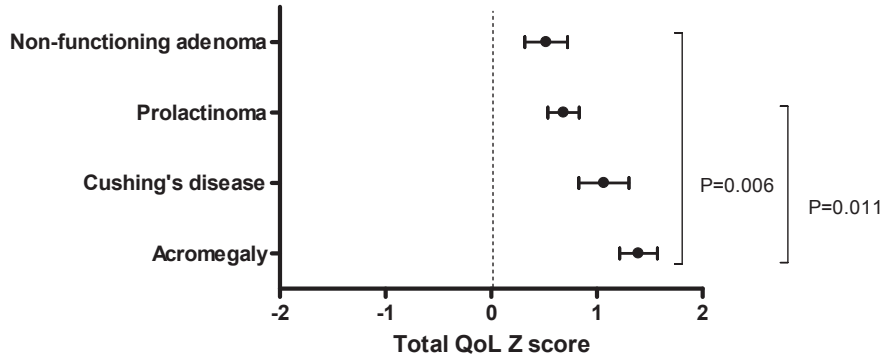

Figure 1

Total quality of life Z-score (mean ± SD) in patients treated for acromegaly (n=118), Cushing's disease (n=58), prolactinoma (n=128), and nonfunctioning macroadenoma (n=99). A higher Z-score denotes a decreased overall quality of life. Perceived quality of life is significantly different between the groups (P=0.003), and is especially decreased in patients treated for acromegaly compared to patients treated for nonfunctioning macroadenoma (P=0.006) and patients treated for prolactinoma (P=0.011).

acromegaly had a larger impairment in physical ability compared to patients treated for nonfunctioning macroadenoma (P=0.004) and to patients treated for prolactinoma (P=0.008).

According to the SF-36, the Z-scores for social functioning, role limitations due to physical problems or emotional problems, general health perception, and change in health did not differ between the different patients groups. However, patients with acromegaly had increased bodily pain compared to patients treated for nonfunctioning macroadenoma (P=0.010), and impairment in physical functioning compared to patients treated for nonfunctioning macroadenoma (P=0.002) and prolactinoma (P=0.037). Patients with Cushing's disease also experienced impairment in physical functioning compared to patients treated for nonfunctioning macroadenoma (P=0.043).

Comparison of Z-scores between patients with pituitary adenomas and patients with paraganglioma (Table 4)

We performed an additional analysis to compare QoL in patients with pituitary adenomas to QoL in patients with another chronic disease: paraganglioma. The comparison between these patients and controls has been published previously (16). Total QoL Z-score was not different between the two groups. Patients with pituitary adenomas had experienced more impairment in role functioning due to emotional and physical problems (SF-36), more pain and impairment in physical ability (NHP) and more general and physical fatigue (MFI-20) compared to patients with paraganglioma.

Table 4. Z-scores (mean ± SD) of QoL in patients treated for pituitary adenomas compared to patients with paraganglioma

Questionnaire	**Pituitary adenomas (n=403)**	**Paraganglioma (n=82)**	**P value**
Total QoL score	1.0 ± 1.7	0.6 ± 1.6	0.150
SF-36			
Physical functioning	-0.9 ± 2.0	-0.5 ± 1.7	0.079
Social functioning	-0.7 ± 1.5	-0.5 ± 1.5	0.454
Role limitations due to physical problems	-0.8 ± 1.5	-0.5 ± 1.3	0.032
Role limitations due to emotional problems	-0.7 ± 1.8	-0.2 ± 1.2	0.003
Bodily pain	-0.5 ± 1.3	-0.3 ± 1.3	0.179
General health perception	-0.7 ± 1.5	-0.5 ± 1.4	0.187
Change in health	-0.2 ± 1.3	-0.1 ± 1.2	0.620
NHP			
Energy	1.2 ± 2.3	0.9 ± 2.9	0.249
Pain	0.9 ± 3.8	0.1 ± 1.2	0.001
Emotional reaction	1.1 ± 4.6	1.0 ± 3.3	0.779
Sleep	0.6 ± 2.0	0.6 ± 2.8	0.918
Physical ability	0.9 ± 2.4	0.2 ± 1.2	<0.001
Social isolation	1.1 ± 3.4	0.8 ± 2.6	0.477
MFI-20			
General fatigue	0.9 ± 1.4	0.5 ± 1.3	0.011
Physical fatigue	1.0 ± 1.5	0.5 ± 1.3	0.008
Reduced activity	0.8 ± 1.5	0.6 ± 1.2	0.116
Reduced motivation	0.6 ± 1.5	0.5 ± 1.1	0.198
Mental fatigue	0.6 ± 1.4	0.6 ± 1.3	0.724
HADS			
Anxiety	0.6 ± 1.4	0.4 ± 1.3	0.360
Depression	0.7 ± 1.8	0.4 ± 1.5	0.135
Total	0.7 ± 1.7	0.5 ± 1.5	0.190

SF-36: higher scores are associated with a better quality of life. NHP: higher score is associated with a worse quality of life. MFI-20: higher scores indicate greater experienced fatigue. HADS: higher scores indicate more severe anxiety or depression.

Influence of disease-specific characteristics on absolute QoL scores within subgroups

Acromegaly: We did not find any significant differences in QoL scores between the patients treated with somatostatin analogs and patients cured after surgery and/or radiotherapy (data not shown).

Prolactinoma: QoL parameters did not differ between patients with a macro- and a microadenoma. QoL parameters did not differ between patients using dopamine agonists and those who did not (data not shown).

Parameters associated with decreased absolute QoL scores (Table 5)

Linear regression analysis was performed in a model using the absolute scores of questionnaire subscales and total QoL score as dependent variables and age, gender, patient group, radiotherapy, follow-up duration, and hypopituitarism as independent variables.

Table 5. Linear regression analysis of absolute QoL scores

Questionnaire	**Age**	**Gender (0=Female, 1=Male)**	**Acromegaly**	**Cushing's disease**	**Prolactinoma**	**Non-functioning macroadenoma**	**Hypopituitarism (0=No, 1=Yes)**	**Radiotherapy (0=No, 1=Yes)**	**Follow-up duration**
Total QoL score		-5.5 (0.015)					4.9 (0.047)		
SF-36									
Physical functioning	-0.6 (<0.001)	6.7 (0.019)	-9.0 (0.012)	-11.5 (0.003)					
Social functioning		6.4 (0.049)				10.4 (0.046)			
Role limitations due to physical problems		12.2 (0.020)							
Role limitations due to emotional problems									
Bodily pain			-9.0 (0.017)						
General health perception			-7.7 (0.042)				-9.8 (0.003)		
Change in health									-0.380 (0.044)
NHP									
Energy							9.9 (0.052)		
Pain		-7.3 (0.009)	10.9 (0.002)	7.8 (0.037)					
Emotional reaction									
Sleep	0.4 (0.003)								
Physical ability	0.5 (<0.001)	-4.8 (0.054)	7.3 (0.019)				5.3 (0.048)		
Social isolation									
MFI-20									
General fatigue		-1.8 (0.006)							
Physical fatigue		-1.3 (0.045)					1.4 (0.048)		
Reduced activity	0.05 (0.037)						1.4 (0.037)		-0.1 (0.028)
Reduced motivation	0.044 (0.047)	-1.4 (0.019)							-0.1 (0.026)
Mental fatigue									-0.1 (0.019)
HADS									
Anxiety		-1.5 (0.004)		1.4 (0.051)					
Depression						-2.1 (0.016)	1.2 (0.038)		
Total									

Unstandardized beta coefficients with p-value in parentheses for independent variables (age, gender, diagnosis, hypopituitarism, radiotherapy, and follow-up duration) and QoL subscales and total QoL as dependent variables. SF-36: higher scores are associated with a better quality of life. NHP: higher score is associated with a worse quality of life. MFI-20: higher scores indicate greater experienced fatigue. HADS: higher scores indicate more severe anxiety or depression.

Age and gender: Age was an independent negative predictor of physical functioning of the SF-36, sleep and physical ability of the NHP, and reduction in activity and motivation of the MFI-20 in patients treated for pituitary adenomas. Male gender was associated with a better QoL with respect to total QoL score, 3 out of the 7 SF-36 subscales (physical and social functioning, and role limitations due to physical problems), the pain and physical ability subscales of the NHP, the general and physical fatigue subscales and reduction in motivation subscale of the MFI-20, and the anxiety subscale of the HADS.

Patient group: Acromegaly was associated with worse scores for physical functioning, bodily pain, and general health perception of the SF-36, as well as for pain and physical ability of the NHP, confirming the results of the comparison between the different patient groups using the Z-scores. Cushing's disease was also associated with increased impairment in physical functioning of the SF-36 and increased bodily pain of the NHP. In addition to the results of the comparison between the different patient groups using the Z-scores, Cushing's disease was associated with increased anxiety scores when linear regression analysis was applied. Nonfunctioning macroadenoma was associated with better scores for social functioning of the SF-36 and depression scores of the HADS. The presence of a prolactinoma did not influence the QoL subscale scores or total QoL score.

Hypopituitarism: The presence of hypopituitarism negatively influenced total QoL score, general health perception of the SF-36, energy and physical ability of the NHP, physical fatigue, and reduced activity of the MFI-20, and depression of the HADS.

Radiotherapy: Previously applied radiotherapy did not influence any of the QoL subscale scores or the total QoL score.

Duration of follow-up duration: Duration of follow-up negatively influenced the change in health subscale of the SF-36 and positively influenced the reduction in activity and motivation and mental fatigue subscales of the MFI-20.

DISCUSSION

In this study, in a very large cohort of patients during long-term follow-up after treatment for different pituitary adenomas, we confirmed that patients with pituitary adenomas suffer from considerably impaired QoL compared to healthy subjects (1-7). The large number of included patients, representing groups with different pituitary tumors, and the specific statistical approach enabled to analyze both general effects of pituitary tumors on QoL as well as the disease-specific effects of individual pituitary adenomas on QoL. We found that patients with acromegaly had the largest impairment in QoL, compared with the other patients with other pituitary adenomas. These differences were mostly due to impairment in physical performance scales and the increase in bodily pain experienced by patients with acromegaly. Patients with Cushing's disease also had impairment in physical functioning compared to patients treated

for nonfunctioning macroadenoma. These data indicate that QoL is impaired during long-term follow-up after treatment of pituitary adenomas in general. Moreover, there are disease-specific impairments in physical functioning (acromegaly and Cushing's disease) and bodily pain (acromegaly). Additionally, linear regression analysis with adjustment for age and gender confirmed these data and extended the disease-specific impairments to increased anxiety in patients with Cushing's disease.

Although many reports of QoL in patients with pituitary adenomas have been published, a considerable methodological problem in the comparison of different pituitary adenomas is formed by the intrinsic differences in age and gender between groups of patients with different pituitary adenomas. Age and gender are major determinants of QoL (12-14). Indeed, the linear regression analysis confirmed the major influences of age and gender on QoL in these specific patients with pituitary adenomas. Calculating age- and gender-specific standard deviation scores for each pituitary disease using a large group of healthy controls enabled us to do a direct comparison. Therefore, our conclusions are not biased by intrinsic differences in age and gender distributions between different pituitary adenomas.

The four health-related questionnaires used in this study, were not disease-specific, *i.e.* they were not developed to assess QoL in acromegaly, Cushing's disease, prolactinoma, or nonfunctioning macroadenoma specifically. This enables us to compare general aspects of QoL between different groups of pituitary adenomas. Nonetheless, there were disease-specific differences in physical functioning subscales. Additionally, anxiety was increased in patients with Cushing's disease.

The impairment of QoL in acromegaly with respect to physical performance scales and to bodily pain is in line with data in a large heterogeneous cohort of 231 patients with active and inactive acromegaly (2), and with a study in another cohort of 39 patients with acromegaly (11). This decreased QoL in patients long-term cured from acromegaly was strongly associated with persisting joint-related co-morbidity (27). Osteoarticular manifestations are present in the great majority of patients at presentation and were also found to be increased compared to the general healthy population in patients with long-term successful biochemical control of acromegaly (27).

In Cushing's disease, both impaired physical functioning and anxiety were increased. This is in line with previous reports on QoL in patients with Cushing's syndrome (28) and QoL after bilateral adrenalectomy for Cushing's disease (29;30). Moreover, in comparison with other pituitary adenomas, patients with Cushing's disease were the most severely affected in all measures of QoL of the SF-36 (11). In addition, Cushing's disease was associated with increased anxiety. Supraphysiological levels of cortisol can induce psychiatric, psychological, emotional, and cognitive disturbances, which can persist even after cure of Cushing's syndrome (31-33). Although data on putative effects of hypercortisolism on brain structures are scarce, Cushing's disease is associated with reduced hippocampal volume (34;35). This cerebral atrophy is partially reversible on MRI after long-term correction of hypercortisolism. However, it is not known,

whether the neural changes are fully reversible and/or correlated with neuropsychological improvement.

Our data indicate that in patients with acromegaly and Cushing's disease QoL is the most severely impaired during long-term follow-up of successful biochemical disease control. However, patients with prolactinoma and patients with nonfunctioning macroadenoma also experienced impairments in health-related QoL in almost all subscales. The overall impairment in all patient groups points towards a strong effect of the pituitary diseases in general on health and well-being, of both the physical and the psychosocial aspects. Indeed, even in comparison to patients with another unrelated chronic disease, *i.e.* paraganglioma, which also requires frequent hospital visits and intensive monitoring, several aspects of QoL are impaired in patients with pituitary adenomas.

Various aspects of pituitary adenomas have been linked to an impaired QoL, including radiotherapy (2;8;9;36), transcranial pituitary surgery (4), and pituitary deficiencies (10). Detailed analysis of factors influencing QoL in the total cohort revealed that male gender was associated with a better QoL compared to women. Hypopituitarism was associated with impairment in QoL in multiple subscales of the different questionnaires. In our patients, we aimed at optimal hormonal substitution of pituitary deficiencies. However, optimal hormonal substitution therapy does not reproduce the normal plasma hormone profiles of healthy individuals. Consequently, titration of endocrine replacement therapy is possible only within certain physiological limits (37). These intrinsic imperfections in endocrine replacement therapy may result in subtle physiological derangements, which could explain the negative influence of hypopituitarism on QoL in this study.

The strategy for obtaining controls was to ask each patient to provide a control person of comparable age and gender from the same socio-economic area. The Leiden University Medical Center is a tertiary referral center for patients with pituitary tumors in the Netherlands, which is a very small country. Therefore, all controls were derived from the same area. The response rate of the control group was 53% for acromegaly, 67% for the nonfunctioning macroadenoma, 57% for Cushing's disease, and 64% for prolactinoma. In addition, the control group was extended by controls derived from other studies in our centre that applied a similar strategy (15-17). Controls might be subject to a selection bias, because patients might have chosen controls with a supposed good health status or controls who had better health may have responded more eagerly to participation (38). However, in previous studies we also compared the outcomes of the same quality of life assessments in our patients to those published for the general Dutch population, which did not affect our conclusions obtained by the use of our own controls (8-10). Therefore, it is very unlikely that the large discrepancies between the patients and the controls in the present study are merely caused by selection bias.

In conclusion, QoL is impaired in patients with pituitary adenomas during long-term follow-up after treatment. In patients previously treated for acromegaly or for Cushing's disease, physical functioning is permanently impaired to a greater extent than in patients with other pituitary

adenomas. Additionally, anxiety is increased in patients previously treated for Cushing's disease. This study thus provides both evidence for general effects of pituitary tumors on QoL, independent of the underlying disease, and disease-specific impairments in QoL. It is essential for doctors to recognize these irreversible effects of pituitary adenomas on QoL despite cure/biochemical control, optimal treatment and/or replacement strategies. It is important to inform patients with pituitary adenomas on these persistent adverse effects of their disease on QoL to prevent inappropriate expectations with respect to the long term results of treatment.

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Chapter 6

MALIGNANT PROLACTINOMA: CASE REPORT AND REVIEW OF THE LITERATURE

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Eur J Endocrinol 2006;155:523-534

ABSTRACT

Pituitary carcinomas are extremely rare. In general, the initial clinical, biochemical, and histological characteristics are of minimal utility in distinguishing benign adenomas from pituitary carcinomas. We describe a 63-year old woman with a macroprolactinoma, who presented with diplopia and blurred vision. This unusual initial presentation and the subsequent aggressive clinical course, with diffuse local and distant intramedulary metastases, prompted us in retrospect to make a detailed analysis of the therapeutic interventions and histology. In addition, we reviewed all available literature on published cases of malignant prolactinoma and detailed their epidemiological, clinical, and histopathological characteristics. In brief, it is postulated that pituitary carcinomas arise from the transformation of initially large, but benign, adenomas. Unusual and/or atypical clinical manifestations appear to occur more frequently. *In vivo*, the development of dopamine agonist resistance in invasive macroprolactinoma is indicative of malignancy and should prompt the clinician to perform a biopsy of the tumor. For pituitary tumors that exhibit high mitotic activity, increased Ki-67 and/or p53 immunoreactivity, it may be useful to denote these tumors as "atypical" prolactinomas to raise the possibility of future malignant development.

INTRODUCTION

Although pituitary tumors are relatively common, occurring in approximately 10-20% of normal subjects on autopsy or magnetic resonance imaging (MRI), the incidence of pituitary carcinoma is extremely low (1). To date, a total of approximately 140 cases have been reported, one-third of them being malignant prolactinomas (2). The histological, clinical, and biochemical characteristics are reported to be of minimal utility in distinguishing benign from malignant tumors, unless (distant) metastases have developed. Presently, it is postulated that pituitary carcinomas arise from the transformation of initially large but benign adenomas (1). The arguments are based on observations that the initial presentation is not different from other macroadenomas, the long-duration needed for the transformation into carcinoma, and the increasing accumulation of genetic aberrations (3). We describe a patient with a malignant prolactinoma, whose unusual initial presentation and clinical course prompted us in retrospect to make a detailed analysis of the case with respect to the therapeutic interventions and histology. For comparison, we reviewed all published cases of malignant prolactinoma and detailed their epidemiological, clinical, biochemical, and histological characteristics.

CASE REPORT

A 63-year old woman, who presented with diplopia and blurred vision, was diagnosed with a macroprolactinoma in 1998. On neurological examination, ptosis of the right eye was present together with abducens palsy and impaired convergence. Furthermore, bitemporal

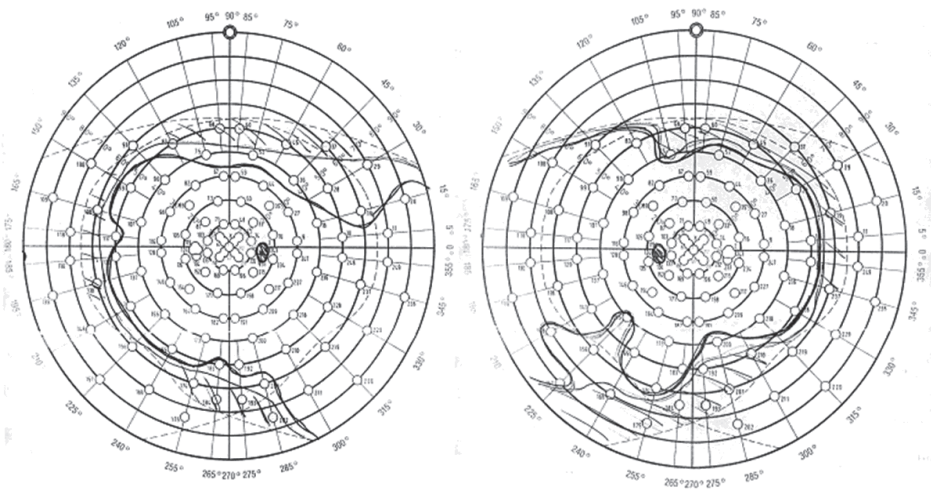

Figure 1.
Visual field investigation in October 1999, revealing bitemporal hemianopsia.

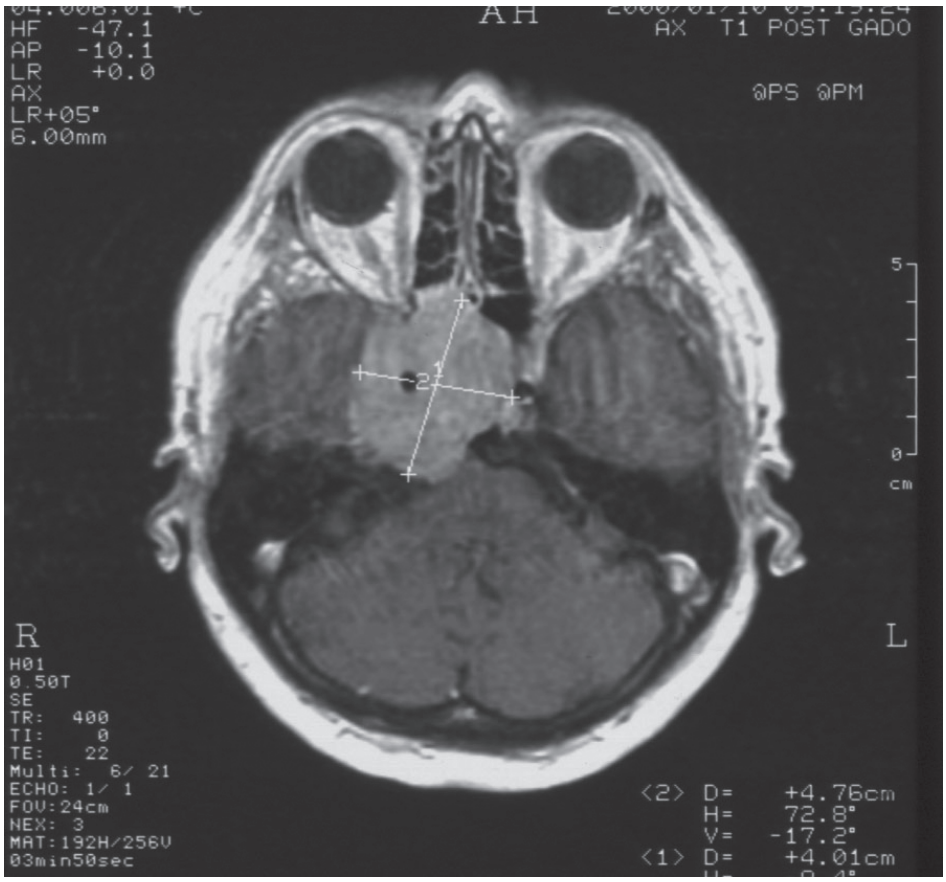

Figure 2.

MRI (axial T1-weighted image) obtained in April 1999, demonstrating a pituitary mass of 2.5 cm, invading the right sphenoidal and cavernous sinus (Hardy classification IV-E, (47)) and encasement of internal carotid artery.

hemianopsia was present (Fig.1). Prolactin concentration was increased 20-fold: 490 µg/L (normal value < 22 µg/L). MRI showed a pituitary mass with a diameter of 2.5 cm, extending into the right sphenoidal sinus as well as into the cavernous sinus and compressing the temporal lobe (Fig.2). Therapy was initiated with bromocriptine (1.25 mg t.i.d) resulting in normalization of the visual fields and decrease in prolactin levels to 56 µg/L within a few months.

The visual field defects recurred and prolactin levels increased to 206 µg/L (Fig.3), six months later. Therefore, bromocriptine treatment was switched to quinagolide (up to 300 µg/day). Nonetheless, in January 2000, MRI showed progression of the pituitary tumor with encasement of the internal carotid artery and compression of the optic chiasm. The macroprolactinoma did not react satisfactory to medical treatment, even with cabergoline, which was stopped, since prolactin levels progressively increased in the presence of further progression of tumor growth. Furthermore, she developed progressive anterior pituitary insufficiency (*de novo* ACTH and TSH

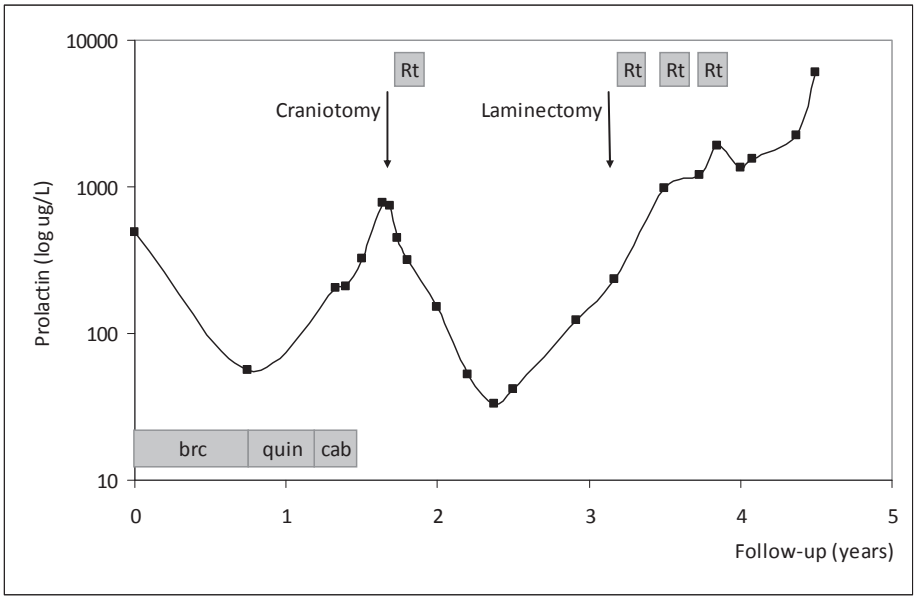

Figure 3.

Serum prolactin concentrations from October 1998 to April 2003 (normal value < 22 µg/L).
Brc, bromocriptine; quin, quinagolide; cab, cabergoline; Rt, radiotherapy.

deficiency) and the visual field defects increased. Therefore, she was operated in April 2000. Decompression of the optic chiasm was performed via transcranial route. Histological investigation of the tumor revealed positive immunostaining for prolactin without mitotic activity, but high Ki-67 (MIB-1) labeling index (10%-15%). Fractionated conventional radiotherapy was administered by a linear accelerator (6 MeV) in a total dose of 54 Gray (Gy) in June 2000. Thereafter, prolactin concentrations decreased gradually without dopaminergic therapy from 445 µg/L in June 2000 to a nadir of 33 µg/L in February 2001 (Fig.3). The effect of tumor volume in response of radiotherapy was evaluated 8 months after radiotherapy with MRI. A slight reduction in tumor volume was noted. Encasement of the internal carotid artery persisted.

Serum prolactin levels started to rise again in August 2001. MRI of the brain did not reveal progression of the tumor, but the rise in prolactin concentration proved to be due to metastases in the spinal cord (Fig.4), which was confirmed with epidepride (dopamine D2 receptor) scintigraphy (Fig.5). Laminectomy was performed in December 2001 because of compression of the myelum in the sacral region, followed by fractionated radiotherapy (6 x 4 Gy) from L5 to S5 in February 2002. Histological examination confirmed a prolactin producing metastasis.

Subsequently, the patient developed extensive metastases throughout the spinal cord. Therefore, the spinal cord was irradiated with fractionated radiotherapy aimed at C2 to L4 with a total dose of 40 Gy in June 2002 to relieve pain and prevent paralysis from compression of the myelum.

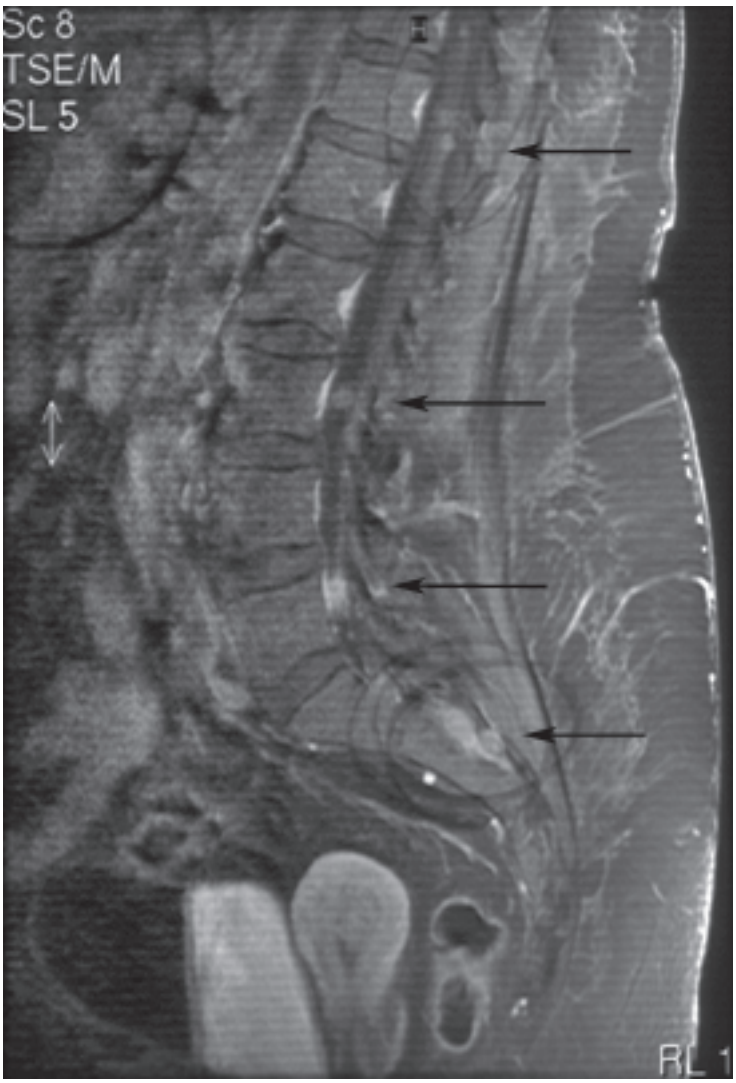

Figure 4.
MRI (sagittal T1-weighted image) obtained in November 2001, demonstrating spinal lesions (arrows) in the lumbar and sacral region.

In August 2002, she developed progressive ptosis of the right eye and facial paralysis due to infiltration of the tumor into the orbital cavity. Repeat radiotherapy to the skull (total dose of 25 Gy) was given in September 2002, resulting in only partial improvement of visual disturbances. However, prolactin concentrations continued to increase (Fig.3) to a final prolactin concentration of 6000 µg/L in May 2003, 1 month before she died at home. Autopsy was not performed.

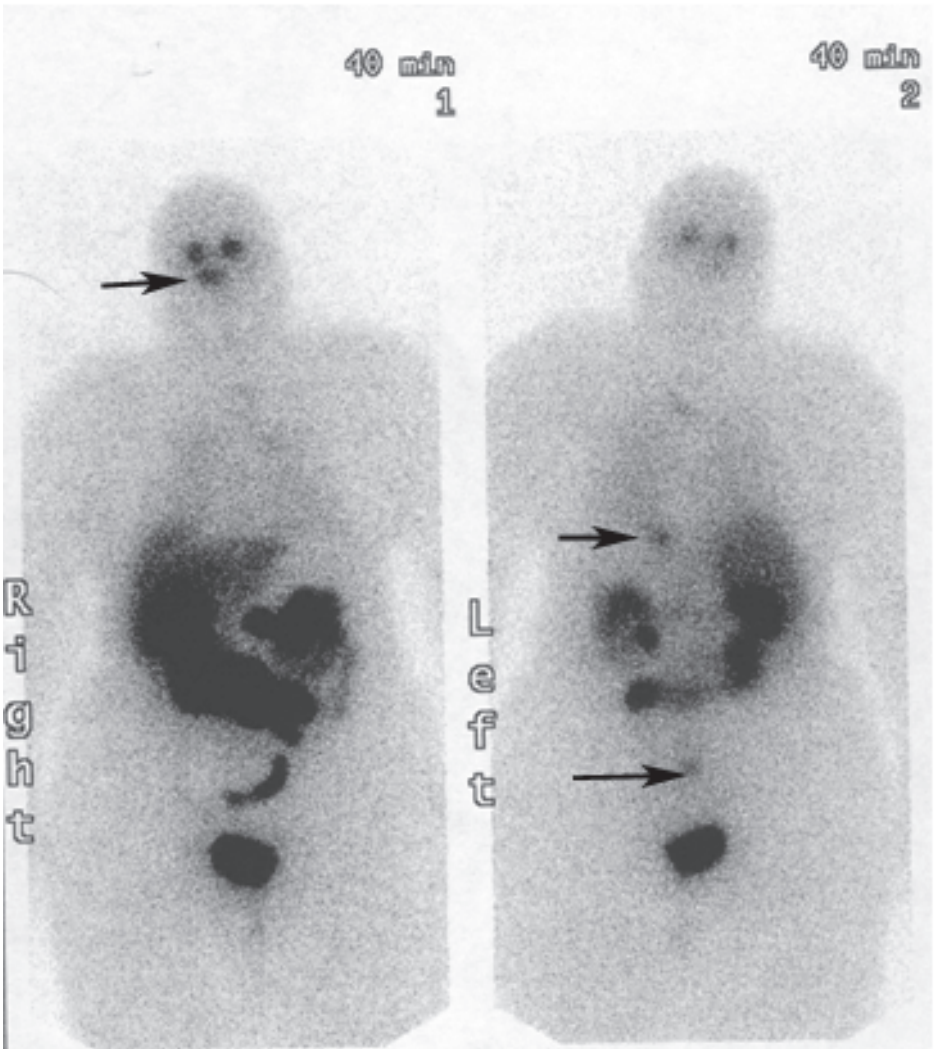

Figure 5.
Total-body scintigraphy after [^{123}I] epidepride injection in December 2001. Physiological accumulation of activity in basal ganglia, liver, kidneys, bowel, and urinary bladder. Anterior view (left image): intracranial accumulation of the isotope reflecting the macroprolactinoma (arrow). Posterior view (right image): multiple accumulations of the isotope reflecting multiple metastases in the spine (arrows).

DISCUSSION

Pituitary carcinomas are considered to arise from the transformation of initially large, but benign adenomas (1). This notion is based on observations that demonstrate that the initial presentation of pituitary carcinomas does not differ from other (invasive) macroadenomas, the long-duration needed for transformation into a carcinoma, and the progressive accumulation

of genetic aberrations (3). The present case of malignant prolactinoma is consistent with many, but not all, of these observations. This gave us the opportunity to compare carefully the data of our patient and review the intriguing features associated with malignant transformation of pituitary prolactinomas.

To date, only 47 cases of malignant prolactinoma have been reported, summarized in Table 1 (4-41). The first report of a patient with a malignant prolactinoma was in 1981 by Martin *et al*. (4). Of the reported cases, 65% were male and the mean age at presentation was 44 years with a range 14-70 years (Table 2). The presenting symptoms were related to hyperprolactinemia in 35% of the reported cases, including amenorrhea, galactorrhea, impotency and decreased libido. At presentation, 71% of the patients had symptoms of local compression, such as headache and bitemporal hemianopsia. Only five other patients presented with ptosis (27;40), diplopia (34), oculomotor paresis (17) or lateral rectus paresis (13). Diabetes insipidus was a feature in only one patient (12). The treatment modalities after diagnosis were transsphenoidal or transcranial surgery (96%), radiotherapy (79%), chemotherapy (2%) and dopamine agonists (DA) in 65% of the cases (Table 3). A study by Isobe *et al*. shows that, in particular, large prolactinomas are very difficult to control with radiation doses between 50 and 60 Gy (42). Therefore, even benign prolactinomas do not respond very well to radiotherapy. The effect of radiotherapy on malignant prolactinoma has not been systematically documented. Therefore, a small response to radiotherapy, as in our case, cannot be interpreted as an indication of the malignant nature of the tumor. The presentation of our patient with diplopia and blurred vision is a very unusual manifestation of pituitary macroadenoma. Such a presentation is most frequently associated with pituitary apoplexia. In the absence of apoplexia, nerve paralysis is strongly suggestive for compression or infiltration of the nerve, secondary to the high proliferative activity of the tumor. The presentation with diplopia as a result of oculomotor nerve paralysis has been reported previously in only one other case (17). In the present case, oculomotor nerve paralysis was due to tumoral orbital invasion (Fig. 2). Orbital invasion of a pituitary adenoma is very uncommon, being reported in only 16 patients, and only 2 of these also manifested diplopia (43). Thus, in retrospect, the initial clinical and radiological presentation was highly indicative for an adenoma with high infiltrative potency.

Kaltsas *et al*. described histological and immunohistochemical parameters that predict the biological behaviour of pituitary tumors (1;3). Histological parameters associated with an atypical or aggressive behaviour of the adenoma are cellular atypia, nuclear pleomorphism, more than two mitotic figures per ten high-powered fields, a proliferative index of Ki-67 more than 3%, positive p53 immunoreactivity, and invasion. They are also called atypical parameters. Histological investigation of the tissue initially obtained by surgery, biopsy, or autopsy of the prolactinoma revealed a benign classification in 37%, and an atypical classification in 40% (Table 3). In the remaining 23% of cases, no documentation of the histological findings was given. The histological investigation in our case demonstrated a prolactinoma with high proliferative index, such as nuclear pleomorphism and high Ki-67 labeling index. Estimation of the cell cycle-

specific antigen Ki-67, using the MIB-1 antibody, has demonstrated to correlate best with invasiveness and probably prognosis (1). Malignant and invasive tumors exhibit much higher Ki-67 labeling indices than benign adenomas (11.9% *vs*. 4.66% *vs*. 1.37%, respectively) (44), although there is considerable case-to-case variability (1). Others even suggested that an increased Ki-67 labeling index is associated with secondary resistance or escape to DA treatment (45).

Table 1. List of previously published cases of malignant prolactinoma

Author, year of publication	Age/ Sex	Primary Treatment*	PA primary tumor	Time interval diagnosis – metastases (years)	Metastatic sites	Treatment of metastases*	PA metastases	Cause of death	Time interval diagnosis – death (years)
Martin, 1981	31/F	TSS, Rt, CT, DA, Rt	Pleomorphism, rare mitotic figures	5.5	Cerebellum	CT	Numerous mitotic figures	Death due to disease progression	8.5
Cohen, 1983	70/M	-	No mitotic figures †	3.5	Cerebellopontine angle	-	No mitotic figures †	Pulmonary oedema, circulatory shock	3.58
U, 1984	63/M	CT, Rt	Mitosis 3/20 HPF	6	Cerebrum	CT, Rt, DA	Mitosis 11/20 HPF, pleomorphic	Pulmonary embolus	6.25
Gasser, 1985	28/M	CT, Rt, DA	Mitosis, pleomorphism	9	Cerebrum	CT, DA, Rt, CT	Mitosis, pleomorphism; tumor cells in subarachnoidal space and in venous blood channels	Death due to disease progression	12
Landgraf, 1985	44/F	CT, Rt, DA	Benign	4	Cerebellum, spinal cord	LT, Rt, DA, Chemo, Octapeptide-somatostatin, Chemo	Benign	Death due to disease progression	5.5
Plangger, 1985	28/M	CT, Rt	Benign	9	Cerebrum, subarachnoid nodules	CT, DA, Rt, CT	Mitotic figures rare	Still alive at publication	
Scheithauer, 1985	52/F	Rt, CT, TSS(2x), DA	Mitotic figures rare	11	Cerebrum, vertebrae, occipital bone, ribs	DA, Rt(2x)	Mitotic figures rare ‡	Death due to disease progression	13.5
Von Werder, 1985	43/F	CT, Rt, DA	Not documented	4	Spinal cord	DA, LT, Rt, DA	Not documented	Unknown	
Muhr, 1988	14/M	CT, Rt	Benign	12	Cerebellum, frontal lobe	Surgery, DA	Mitosis	Still alive at publication	
Atienza, 1991	34/M	DA, CT(2x), Rt, DA	No mitotic figures	4	Spinal cord, pulmonary nodules	DA, Rt, TSS	Mitosis 2/10 HPF, vascular invasion	Death due to disease progression	5.5
Popovic, 1991	47/M	DA, CT(2x), Rt	Mitosis 6/HPF	2	Dura, cerebrum, cerebellum	CT	Mitosis 6/HPF	Gastrointestinal bleeding	2.02
	56/F	TSS, Rt	Mitosis 5/10 HPF	12	Roof fourth ventricle, cerebrum, spinal cord	CT	Mitosis 5/10 HPF	Acute pulmonary oedema, S. Aureus septicemia	12.33
Berezin, 1992	32/F	CT, Rt	Benign	20	Intraorbital	CT, enucleation left eye and retroorbital mass, Rt	Mitosis 3-4/10 HPF, pleomorphism	Anorexia, pneumonia, comatose, death due to disease progression	25
Figarella, 1992	45/M	TSS, DA, CT(2x)	Mitosis 1/2 HPF	8	Vertebrae, lung	-	Not documented	Unknown	
Kamphorst, 1992	45/M	CT, Rt, Chemo, Rt	Mitotic figures rare	13	Pons, medulla oblongata, spinal cord	-	Mitotic figures rare †	Death due to disease progression	13.02
Petterson, 1992	40/M	CT, Rt, DA	Mitotic figures	5	Encasement carotid bifurcation, retro-orbital space, cerebrum, cerebellopontine angle, nodule vertebral artery	CT, DA, CT, Chemo, CT, Chemo	Pleomorphic, invading overlying cerebral tissue	Death due to disease progression	8

Author, year of publication	Age/ Sex	Primary Treatment*	PA primary tumor	Time interval diagnosis – metastases (years)	Metastatic sites	Treatment of metastases*	PA metastases	Cause of death	Time interval diagnosis – death (years)
Assies, 1993	63/M	CT, Rt, DA	Not documented	7	Cerebrum	Surgery, DA, Rt	Not documented	Death due to disease progression	8
Kasantikul, 1993	30/F	DA	No mitotic figures †		Pons, subarachnoid space	-	No mitotic figures †	Pneumonia, duodenal ulcer, deep vein thrombosis left leg	0.17
	22/M	CT, Rt	Benign	3	Optic nerves	CT	Mitotic figures in large numbers	Still alive at publication	
Walker, 1993	32/M	TSS, Rt, DA, TSS(4x), CT	No mitotic figures	5	Sphenoidal and ethmoidal sinuses, orbit, liver, lungs, hilar nods	Chemo, TSS, 125I implantation, TSS, DA, Octreo, TSS, Rt, Chemo	No mitotic figures	Pneumonia	9.5
	48/F	Rt, DA, TSS	No mitotic figures	15	Vertebrae, sacroiliac joints, femur	DA, Rt, Chemo	No mitotic figures ‡	Renal failure	15.5
	49/M	CT, Rt	Benign	2	Mediastinal lymph node, lung	DA, CT, Rt, Octreo	No mitotic figures	Pulmonary embolus post-operatively after hip replacement	3.5
Long, 1994	70/M	TSS	No mitotic figures	6	Cerebrum	CT, Rt, CT, Rt, DA	No mitotic figures †	Still alive at publication	
O'Brien, 1995	48/M	CT, Rt, DA	Benign	5	Cerebrum	CT	Mitoses frequent	Still alive at publication	
Gollard, 1995	33/F	TSS, DA, TSS biopsy, Rt	No mitotic figures	12	Cheek pouch, cerebrum, pelvis, ovaries	DA, surgery, Rt, hysterectomy, salpingo-oophorectomy, Chemo	Mitosis 1-3/HPF	Still alive at publication	
Saeger, 1995	59/M	DA, TSS(2x), Rt	Mitotic figures	5	Liver	Chemo, DA	Pleomorphic ‡	Pulmonary embolus	6
Rockwell, 1996	50/M	TSS, CT, Rt, DA	Benign	16	Spinal intradural	Gamma-knife radiosurgery, LT, Rt, DA	Mitotic figures	Still alive at publication	
Bayindir, 1997	32/F	DA, TSS	Mitoses and necroses, pleomorphic	0.08	Oculomotor nerve, the optic foramen, encasement carotid artery, cerebrum, spinal cord	CT, LT, CT	Mitoses and necroses	Death due to disease progression	0.25
Hurel, 1997	49/F	TSS, Rt, DA	Benign, p53 positive	5	Ethmoidal sinuses, orbita, temporal fossa, pons, maxillary antrum, submandibular node	CT, Rt, DA, Octreo, Chemo	Pleomorphic, p53 positive, Ki-67 positive	Tumor infarction or hemorrhage, coma	7
Pernicone, 1997	44/F	TSS, Rt	Not documented	3	Oral submucosa, ovaries, myometrium, pelvic nodes	Surgery, Rt, Chemo, DA	Not documented	Still alive at publication	
	34/M	DA, Rt, TSS	Not documented	3	Vertebrae, femur	Rt	Not documented	Death due to disease progression	4
	62/M	CT, Rt	Not documented	3	Cerebellum	Rt, DA, Surgery	Not documented	Death due to disease progression	11
	54/F	TSS	Not documented	1	Spinal subarachnoid	Rt, DA, Chemo	Not documented	Death due to disease progression	3
	37/M	TSS(2x)	Not documented	6	Lymph nodes	Rt	Not documented	Death due to disease progression	7
	64/M	TSS	Not documented	6	Occipital lobe, tentorium	Unknown	Not documented	Still alive at publication	

Author, year of publication	Age/ Sex	Primary Treatment*	PA primary tumor	Time interval diagnosis – metastases (years)	Metastatic sites	Treatment of metastases*	PA metastases	Cause of death	Time interval diagnosis – death (years)
Popadic, 1999	51/M	CT, DA, Rt	Invasive prolactinoma, pleomorphism, no mitotic figures	4	Spinal cord	TSS, LT, Rt, DA	Pleomorphism with rare mitotic figures, tumor cells in nervous and fibrous tissue	Still alive at publication	
Arias, 2000	32/M	DA, CT, Rt	Mitosis	1	Medulocerebral angle, vertebrae, spinal epidural space	CT, Rt	Mitosis; tumor cells in subarachnoid space and in venous blood channels	Pneumonia	3
Petrossians, 2000	43/M	CT, TSS(2x), DA	Not documented	7	Spinal cord, rib, mediastinum, femur	CT, Rt, DA, gamma-knife radiosurgery(4x), CT(2x), Rt	Not documented	Death due to disease progression	15
Sironi, 2002	45/M	TSS, CT, TSS, Rt, Sandostatin	Mitosis 1/20 HPF	9	Cerebrum, spinal cord	CT(2x), Rt	Mitosis 5-25/10 HPF, Ki-67 positive, pleomorphic	Pulmonary embolism	10.42
Vaquero, 2003	40/M	CT, Rt	Not documented	14	Cerebrum	Surgery	Ki-67 < 2%	Still alive at publication	
Winkelmann, 2002	53/M	DA, TSS, CT, Rt	Pleomorphism, Ki-67 positive	6	Orbita, foramen magnum, medulla oblongata, spinal cord, vertebrae	DA, gamma-knife radiosurgery(2x)	Pleomorphic, Ki-67 positive †	Renal failure, lung oedema, death due to disease progression	7
Harinarayan, 2004	26/M	CT, DA	Benign	7	Liver, gastric	DA, Octreo	Benign ‡	Unknown	
Lamas, 2004	14/M	TSS, DA, Rt, CT	Pleomorphism, numerous mitotic figures	6	Cerebrum, skull, pulmonary hilum, nodules lungs,ribs, pelvis, spine	Chemo, DA	Mitotic figures ‡	Still alive at publication	
Noda, 2004	52/F	TSS, CT, Rt, DA	Benign	7	Cerebellum, medulla oblongata, spinal cord	Gamma-knife radiosurgery, Rt, DA	Pleomorphism, Ki-67 positive ‡	Respiratory arrest	9
Uum Van, 2004	20/F	CT(2x), DA	Not documented	13	Leptomeningeal	LT, DA	Low mitotic index	Still alive at publication	
Vaishya, 2004	55/F	CT, Rt, DA	Benign	10	Encasement internal carotis artery, sphenoid sinus	TSS, DA	Mitosis 2/10 HPF, vascular invasion, Ki-67 positive	Death due to disease progression	11
Crusius, 2005	47/M	TSS, CT, Rt, DA	Ki-67 2.80% and 4.40%	6	Cerebrum		Ki-67 4.45% ‡	Cardiac arrest	6.02
Kars, 2006	62/F	DA, CT, Rt	No mitotic figures, Ki-67 10-15%	3.5	Sinus sphenoidales, encasement internal carotis artery, spinal cord, vertebrae	LT, Rt(3x)	Mitosis 6/HPF, Ki-67 positive	Death due to disease progression	5

M, male; F, female; Chemo, chemotherapy; CT, craniotomy; DA, dopamine agonist; HPF, high-powered field; LT, laminectomy; PA, pathological anatomic investigation; Octreo, octreotide; Rt, radiotherapy; TSS, transsphenoidal surgery.

* Number in parentheses indicate number of treatments

† Pathological findings on autopsy

‡ Pathological findings on biopsy

Table 2. Summary of clinical features of malignant prolactinoma presented between 1981 and 2005

n=48		
Gender, male, *%*	65	
Age, *yr*	43.6 (range 14-70)	
Most prevailing symptomatology, *No. (%)*	*Primary tumor*	*Metastases*
Hyperprolactinemia	17 (35)	1 (2)
Local compression	34 (71)	35 (73)
Metastatic sites, *%*		
Intracranial	75	
Extracranial	33	
Extramedullary	40	
Mean time interval diagnosis – metastases, *yr*	6.9 (range 1 month -20 years)	
Mean time interval metastases – death, *yr*	1.9 (range 1 week – 8 years)	
Mean time interval diagnosis – death, *yr*	8.0 (range 2 months – 25 years)	
Alive at publication, *%*	29	

Data are expressed as mean, unless otherwise mentioned. Yr, year.

The time interval between the onset of symptoms at presentation and subsequent metastases in the published cases was highly variable, with a median duration of 7 years, but ranging from 1 month to 20 years. Local recurrence after adenomectomy followed by repeated surgical interventions for local regrowth and extension of the pituitary tumor is frequently observed in malignant prolactinoma. Symptoms of prolactin hypersecretion rarely dominated the clinical picture of metastatic disease. However, symptoms of local compression at the metastatic sites were present in 73% of the cases. In some cases, metastases only manifested during autopsy (14;18;20;21).

Intracranial metastases were reported in the frontal lobe (7;9;12;18;19;22;23;27;33;34), parietal-occipital lobe (6;22;29), temporal lobe (10;18;24;28;33), cerebellum (4;8;12;14;29;38), cerebello-pontine angle (5;18;31), brainstem (17;20;28;38) and subarachnoid space (9;14;20). Less commonly involved areas were the cranial nerves (20;27) and the orbital space (15;18;28;35). Extracranial metastases within the central nervous system involved the spinal cord (8;11;13;14;17;26;27;29-33;35;38;39). Approximately, 40% of the malignant prolactinomas were associated with systemic metastases in bone (10;16;21;29;32;35;37), lymph nodes (18;21;28;29;31;37), lung (13;16;21;31;37), liver (21;25;31;36), and, rarely, ovaries (24;29).

Treatment of metastatic disease consisted of surgery in 69%, radiotherapy in 54%, and chemotherapy in 21% of cases. There is a case-to-case variability of the effect of chemotherapy on prognosis. At publication, three out of ten patients were still alive. Survival time of the remaining seven patients after being diagnosed with metastases was 2.1 years compared with 1.9 years for the whole cohort of patients. The mean time interval of diagnosis until death is 7.8 years compared with 8 years of all reported cases. Although, these data involve only a limited number of cases, we conclude that chemotherapy does not improve prognosis of malignant prolactinoma. In addition, 60% of the patients were treated with dopamine agonists. Only a

minority of the patients was treated with octreotide (8;21;28;36) or gamma-knife radiosurgery (26;32;35;38). Survival in these patients was not different from the other patients.

Histological investigation of the metastatic lesions showed more often tissue with atypical parameters, compared with the results obtained from the primary tumor. Atypical features were present in 62% in the metastatic lesions versus 40% in the primary tumor.

The prognosis of malignant prolactinoma is poor. Survival after the onset of initial symptoms of prolactinoma is approximately 8 years, although there are patients who have survived for as long as 25 years. Only 60% of reported cases with a prolactin-secreting pituitary carcinoma survive more than 1 year after the development of metastases. It is presently difficult to estimate long-term survival in all patients since long-term follow up has not been reported in most of these patients.

Another feature indicative for non-benign clinical course is the disappearance of prolactin-suppressive effects of treatment with DA. DA resistance, or an escape to the prolactin-suppressive effects, during treatment of prolactinoma is rare, but has been reported in the majority of patients with malignant prolactinomas (Table 3). Only six patients, however, including our case, were treated with cabergoline. When non-compliance is ruled out, this phenomenon is associated with dedifferentiation of the tumor and thus of malignant transformation. In our case, it is certainly remarkable because we found positive visualisation of the pituitary tumor and the metastases by the epidepride scan (Fig.5). Apparently, the tumor still expressed the D2 receptors because [^{123}I] epidepride binds with high affinity to dopamine D2 receptors (46). Epidepride scintigraphy was only performed in our case and in only one previously reported

Table 3. Histopathological, biochemical, and therapeutic characteristics of the primary tumor and metastases

n=48	Primary tumor	Metastases	Overall
Histological classification			
Typical	18 (37)	8 (17)	
Atypical	19 (40)	30 (62)	
Not documented	11 (23)	10 (21)	
Response to DA			
DA resistance			15 (31)
Cabergoline			2 (13)
Others			13 (87)
DA escape			25 (52)
Cabergoline			4 (16)
Others			21 (84)
Therapy			
Surgery	46 (96)	33 (69)	
Radiotherapy	38 (79)	26 (54)	
Surgery and radiotherapy	38 (79)	20 (42)	
Chemotherapy	1 (2)	10 (21)	
Dopamine agonist	31 (65)	29 (60)	

Data are expressed as number (percentage). DA, dopamine agonist.

case by Petrossians *et al*. (32). Scintigraphy in the latter detected metastases in the spine, rib, mediastinum, and right femur. The metastases were treated with radiotherapy. In general, it is currently unclear how to translate these results in only two patients to the diagnostic value of this procedure in benign and malignant prolactinomas. The development of pituitary insufficiency within a time frame of several weeks is also consistent with tumor dedifferentiation and growth. The occurrence of pituitary insufficiency within such a short time interval is exceptional in pituitary adenoma.

In conclusion, malignant prolactinoma can present with unusual and atypical clinical manifestations. In the case of an invasive macroprolactinoma, these features, together with the development of resistance to dopamine agonists, should prompt the clinician to obtain histological information. In the presence of atypical indices, such as nuclear pleomorphism, numerous mitosis, and increased Ki-67 labeling index, the prolactinoma could be termed atypical to denote the potential of malignant transformation.

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Chapter 7

GENERAL DISCUSSION AND CONCLUSIONS

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Prolactinomas are characterized by autonomous overproduction of prolactin caused by pituitary adenomas derived from lactotroph cells. Hyperprolactinemia causes symptoms such as infertility, decreased libido, and galactorrhea. In addition to these disease-specific manifestations, mass effects of the pituitary adenoma can lead to symptoms such as headache, visual field defects, and hypopituitarism. Therefore, all patients require treatment aimed at biochemical control of prolactin levels and reducing tumor size, and, subsequently long-term follow-up. Furthermore, patients experience an impaired well-being, mostly due to increased anxiety and depression.

Dopamine agonists are the first choice of treatment since the seventies of the last century. Dopaminergic drugs, especially cabergoline, are effective in inducing normoprolactinemia and reducing tumor size. However, recently, the ergot-derived dopamine agonist cabergoline has been associated with increased valvular heart disease in patients with Parkinson's disease.

In this thesis, several aspects of treatment and long-term follow-up of patients with prolactinomas are addressed.

Long-term outcome of patients with macroprolactinomas initially treated with dopamine agonists

In macroprolactinomas, treatment with dopamine agonists is the first line of therapy, and is capable in inhibiting prolactin secretion, and in reducing tumor volume (1-13). In some patients, however, intolerance due to nausea and postural hypotension limit continuation of dopamine agonists, and additional treatment modalities such as transsphenoidal surgery and radiotherapy are necessary. The immediate biochemical and radiological response to dopamine agonists in macro- and microprolactinomas has been documented extensively in many previous publications (1-13). Remarkably, however, only 4 studies reported long-term follow-up of macroprolactinomas initially treated with dopamine agonists (14-17). However, these studies are incomplete with respect to prevalence rates of pituitary deficiencies, radiological outcomes, and remission rates, and comprised only a small number of patients. Therefore, there were remaining uncertainties with respect to the long-term outcome of patients treated for macroprolactinomas. In **chapter 2**, we described the radiological outcome, pituitary deficiencies, and remission rates after multimodality treatment in patients with macroprolactinomas initially treated with dopamine agonists.

Seventy-two consecutive men and women with macroprolactinomas were initially treated with dopamine agonists. In 65% of the patients, dopamine agonists alone adequately controlled hyperprolactinemia and the macroprolactinoma. Additional treatment with transsphenoidal surgery was necessary in the remaining 35% of the patients, mostly for the reason of dopamine resistance and intolerance. Postoperative radiotherapy was provided in 18% of the patients. Ultimately, control of hyperprolactinemia was achieved in 85% of the patients, although complete remission (*i.e.* normal prolactin levels after the withdrawal of dopamine agonists) was present

in only 22% of all patients during long-term follow-up, and in 33% of the patients following additional transsphenoidal surgery and/or radiotherapy. Overall, pituitary deficiencies of one or more axes occurred in 39% of all patients. Additional therapy increased the prevalence of hypopituitarism of one or more axes from 21% in the patients treated with dopamine agonists only, to 67% in the patients treated with dopamine agonists and subsequent transsphenoidal surgery, and to 77% in the patients who also received postoperative radiotherapy. MR imaging showed regrowth of adenoma in 7% of the patients, whereas a recurrence was noted in 4% of the patients. Tumor shrinkage occurred in 57% of the patients.

This study supports the efficacy of dopamine agonists in the treatment of macroprolactinomas on immediate biochemical control of prolactin levels and tumor growth. Furthermore, these findings support the data reported by previous studies on clinical outcome at long-term follow-up (14-19). Hamilton *et al*. reported remission rate of 27% after surgery in 45 patients with macroprolactinomas resistant to dopamine agonists, whereas the remission rate following surgery reported by Losa *et al*. was ~45% in 61 patients treated for macroprolactinomas (18;19). Additional surgery following dopamine agonists therapy was used in 14-38%, reported by previous studies (14-17), with remission rates of 8% only reported by one study (14). Berinder *et al*. and Wu *et al*. report data concerning additional postoperative radiotherapy, in 14 and 50% of patients, respectively (16;17). Therefore, it seems that additional treatment is required in a relevant proportion of patients with macroadenomas.

Data of hypopituitarism during long-term follow-up are scarce. Apparently, only Chattopadhyay *et al*. described results of hypopituitarism after multimodality treatment, with a prevalence of 55% after 2.6 years of follow-up in 29 men with macroprolactinomas (15). Recurrence of adenoma on imaging during prolonged follow-up in macroprolactinomas has a low frequency. Wu *et al*. found in none of the 14 patients with a giant prolactinoma recurrence after treatment with bromocriptine and/or surgery and additional radiotherapy (17).

The present study has certain limitations inherent to the retrospective study design that should be taken into account. The patients are derived from a historical cohort, and, in the past, patients have been treated with the only available dopamine agonist bromocriptine for several years. Bromocriptine, compared to cabergoline has some disadvantages, such as the short half-life, and the frequent occurrence of side effects. As a consequence, compliance of the patients treated with bromocriptine was less compared to patients treated with cabergoline, resulting in repeating recurrences of hyperprolactinemia after withdrawal of bromocriptine, and leading to additional therapies such as transsphenoidal surgery. It is likely that the results would have been slightly better if all patients would have been treated with cabergoline, which has a higher efficacy and a lower incidence of adverse effects (5;6;20). However, even cabergoline is associated with failures with respect to the adequate medical treatment of macroprolactinomas, estimating to be 10-20% (21;22). Even though not all our patients used cabergoline, our study is unique with respect to the long-term follow-up of patients with macroprolactinomas treated

initially with dopamine agonists, and the effects of multimodality treatment on endocrine and radiological outcome.

In our center, different pituitary adenomas have been evaluated at long-term follow-up after multimodality treatment (23;24). A summary of the data described in these studies, concerning acromegaly, Cushing's disease, nonfunctioning macroadenomas, and the data of the present study on macroprolactinomas are shown in Table 1. Patients diagnosed with acromegaly, Cushing's disease, or nonfunctioning macroadenomas were all treated by primary transsphenoidal surgery. Postoperative radiotherapy was applied to prevent recurrence in nonfunctioning macroadenomas, or to treat persistent disease in acromegaly or Cushing's disease, or to treat recurrent disease in acromegaly, Cushing's disease, or nonfunctioning macroadenomas.

Table 1. Long-term follow-up after multimodality therapy of different pituitary adenomas in one center

	Acromegaly	**Cushing's disease**	**Nonfunctioning macroadenoma**	**Macro-prolactinoma**
No. of patients	164	74	174	72
Study period	1977-2002	1977-2005	1977-2005	1980-2004
M/F, *No.*	91/73	18/56	98/76	33/39
Age*, *yr*	47	39	55	39
Duration of follow-up, *yr*	12	13	9	10
Treatment				
Medication†, *%*	13	-	-	100
Surgery, *%*	100	100	100	35
Radiotherapy, *%*	34	19	36	18
Outcome				
Hypopituitarism, *%*	32	44	93	39
Recurrence, *%*	9	16	16	4
Remission, *%*	88	93	84	22
SMR	1.33	2.39	1.24	not available

Data are expressed as mean, unless otherwise mentioned. Definition of hypopituitarism: pituitary deficiency of one or more axes. Definition of recurrence: biochemical recurrence with increase of growth hormone level above 2.5 µg/L (5 mU/L) in patients with acromegaly; biochemical recurrence of hypercortisolism in patients with Cushing's disease (*i.e.* insufficient suppression of plasma cortisol to 1 mg oral dexamethasone (cortisol > 100 nmol/L the following morning) and/or abnormal 24-h urine free cortisol excretion on two consecutive samples); radiological recurrence with appearance of tumor mass without residual tumor mass on a previous MRI in patients with nonfunctioning macroadenomas and macroprolactinomas. Definition of remission: growth hormone level < 2.5 µg/L in patients with acromegaly; normal suppression to 1 mg oral dexamethasone (cortisol < 100 nmol/L the following morning) and normal 24-h urine free cortisol excretion on two consecutive samples in patients with Cushing's disease; absence of recurrence in nonfunctioning macroadenomas; normal prolactin levels after withdrawal of dopamine agonist in macroprolactinomas. M, male; F, female; yr, year; SMR, standardized mortality ratio.

* Mean age at operation in patients with acromegaly, Cushing's disease, and nonfunctioning macroadenomas; Mean age at diagnosis in patients with macroprolactinomas.

† Medication: treatment with octreotide in patients with acromegaly; treatment with dopamine agonists in patients with macroprolactinomas.

References: (23;24)

Primary medical treatment with somatostatin analogs can presently be considered for patients with acromegaly, and is successful in only ~60% of the patients (25). In contrast, patients with macroprolactinomas are all primary treated with dopamine agonists, reserving transsphenoidal surgery and postoperative radiotherapy as secondary and tertiary treatment modalities, respectively. There are important and impressive discrepancies in endocrine and radiological outcomes in patients with different pituitary adenomas. Patients operated for nonfunctioning macroadenomas suffer from a high prevalence of hypopituitarism of one or more axes (93%), although only 36% of these patients received radiotherapy, comparable to 34% of the patients with acromegaly with a much lower prevalence of hypopituitarism at long-term follow-up (32%). One might suggest that this is related to preoperative tumor size. However, invasive macroadenomas were present in 30% of the patients with nonfunctioning macroadenoma compared to 21% in patients with acromegaly. Furthermore, patients with Cushing's disease were almost all microadenomas (85%), and only 44% developed hypopituitarism at long-term follow-up. Another explanation could be the presence of native (pre-treatment) hypopituitarism. This was present in 85% of the patients with nonfunctioning macroadenomas, but only in 3% and 6% in the patients with Cushing's disease and macroprolactinomas, respectively. Another remarkable discrepancy in outcome is the remission rate. Patients with acromegaly, Cushing's disease, or nonfunctioning macroadenomas have comparable remission rates between 84 and 93% after multimodality treatment. In macroprolactinomas, remission rate after multimodality therapy is only 22%, although 85% of the patients have a normal prolactin level with or without dopamine agonists. Apparently, remission rates after initially treatment with dopamine agonists for macroprolactinomas is not comparable to the remission rates by treatment of other pituitary adenomas. Hence, the long-term consequences of treatment of macroprolactinomas are considerably different from that of the other pituitary adenomas.

Clinical implications. Dopamine agonists are the first line of therapy for macroprolactinomas, resulting in normalizing prolactin levels in 85%, inducing tumor shrinkage in 57%, and long-term remission rates in only 22% of the patients. Additional transsphenoidal surgery should be reserved for patients with dopamine agonist resistance or intolerance. Considering the high prevalence of hypopituitarism following radiotherapy, this therapy should be carefully considered, and rather be indicated for mass control than for hyperprolactinemia. Although the recurrence rate is low in macroprolactinomas, these findings indicate that patients with macroprolactinomas require long-term dedicated care.

Prevalence of valvular heart disease in patients treated several years with dopamine agonists for prolactinomas

The ergot-derived dopamine agonists cabergoline and pergolide are potent agonists of the 5-HT_{2b}-receptors, with a high binding affinity for these serotonin receptors, compared to bromocriptine and lisuride. Stimulation of 5-HT_{2b}-receptors, which are highly expressed on cardiac valves, activates fibroblast mitogenesis, leading to valvular fibrosis, valvular thickening, and subsequent to valvular regurgitation. Furthermore, several studies have reported an increased

prevalence of clinically relevant regurgitation requiring valve replacement during the treatment of cabergoline and pergolide in patients with Parkinson's disease (26-32). The cardiac abnormalities in these patients resemble the manifestations seen in patients treated with anorectic drugs, or antimigraine ergot alkaloids drugs, or in patients with serotonin-secreting carcinoid tumors (33-37). To date, no data have been published concerning the treatment with cabergoline in patients with prolactinomas. In prolactinomas, cabergoline is used at a much lower dose, but for a much longer time compared to patients treated for Parkinson's disease. Furthermore, there are considerable differences in gender and age distributions between patients with prolactinomas and Parkinson's disease, which hamper a proper comparison. As a consequence, questions regarding the safety of dopamine agonists, and especially cabergoline, for the treatment of prolactinomas emerged.

Therefore, in **chapter 3**, we assessed the prevalence of valvular regurgitation and valvular morphology in 78 patients with prolactinomas by two-dimensional and Doppler echocardiography study. We compared these data with 78 control subjects, matched for age, gender, body surface, and left ventricular systolic function, recruited from an echocardiographic database. Of these 78 patients, 47 patients were treated with cabergoline (mean period of 5.2 years, mean cumulative dose of 363 mg), and were compared with 31 patients not treated with cabergoline (*i.e.* they were treated with bromocriptine, terguride, quinagolide, or no dopamine agonist at all) to exclude the influence of disease-specific aspects. The prevalence of clinically relevant valvular regurgitation was not increased in patients treated for prolactinomas compared to control subjects. However, mild tricuspid regurgitation and calcification of the aortic valve was more prevalent in patients with prolactinomas compared to control subjects.

The main problem with the present study was that most of the patients treated with cabergoline, had previously been treated with other dopamine agonists. Therefore, other studies with a more clear separation between cabergoline users and users of other dopamine agonists are warranted.

Two patients treated with cabergoline had, by coincidence, bicuspid aortic valve. One of these two patients had severe aortic regurgitation, which was an indication for cardiac surgery. Aortic root replacement was performed with stentless valve implantation. The thoracic surgeon observed macroscopic changes of the aortic leaflets, which consisted of calcifications and thickening. Pathological examination of the ascending aorta showed minor fibrotic thickening of the intima. This 46-year old male patient had been treated with cabergoline for 8.5 years, with a cumulative dose of 362 mg (mean weekly dose of 0.8 mg). He was diagnosed with macroprolactinoma 13 years prior to echocardiography, and he was initially treated with another dopamine agonist quinagolide. He is a current smoker, with a BMI of 23 kg/m^2, blood pressure of 111/69 mmHg, normal prolactin levels and normal serum cholesterol and LDL levels.

The ***clinical implications*** of this increased prevalence of mild tricuspid regurgitation and calcification of the aortic valve in the absence of increased clinically relevant valve regurgitation are insecure. Cabergoline seems to be safe in patients with prolactinomas, since there is no

increased prevalence of significant valve regurgitation in patients with prolactinomas using the "low-dose" of cabergoline, in contrast with patients with Parkinson's disease using the "high-dose" of cabergoline. Therefore, at present there is no indication to replace cabergoline with another dopamine agonist. However, we can not exclude the possibility that long-term low-dose use of cabergoline induces fibrotic changes in cardiac valves, of which the thickening and calcifications might be an early sign. Additional studies with more patients and a longer use of cabergoline are warranted. Furthermore, baseline echocardiography is advisable to prevent prescription of cabergoline to patients with pathological pre-existing cardiac valve conditions.

Assessments of quality of life parameters in patients treated for prolactinomas and compared with patients with other pituitary adenomas

Recently, health-related quality of live has received considerable attention in the treatment of many diseases. The impact of endocrine diseases on psychological and social well-being is far more difficult to document, in contrast to physical complaints and well-being. Although a wide variety of chronic diseases are associated with impaired quality of life, the direct physical and psychosocial influences of hormonal excess or deficiencies distinguish endocrine diseases, and also pituitary diseases, from other diseases. Subtle derangements of psychological and social well-being can hardly be assessed in clinical practice, whereas they have a tremendous impact on the patient. This may also affect the patient-doctor relationships, because these complaints may not be appreciated into the proper perspective by the doctor. Therefore, we assessed quality of life parameters in large cohorts of consecutive patients treated for pituitary adenomas in our center.

Four validated, health-related quality of life questionnaires were used to assess quality of life in all patients with different pituitary adenomas: Short-Form-36 (SF-36), Nottingham Health Profile (NHP), Multidimensional Fatigue Inventory (MFI-20), and Hospital Anxiety and Depression Scale (HADS). Patient outcomes were compared to the results of control group with equal age and gender distribution, and derived from the same geographical area with comparable social-economic status. The purpose of these studies described in **chapter 4 and 5** was to evaluate various physical and psychological aspects of quality of life in patients with prolactinomas and to evaluate disease-specific impairments in patients with different pituitary adenomas.

We included patients with long-term cure or biochemical control of acromegaly, Cushing's disease, or nonfunctioning macroadenoma. In these patients, our group has previously documented that quality of life parameters were impaired compared to control subjects. Factors influencing the negative impact of these diseases on physical and psychological well-being include irreversible effects of previous hormone excess, radiotherapy, and hypopituitarism (38-40). Because we were curious to understand the impact of treatment and follow-up of a pituitary adenoma in patients without the influences of surgery or radiotherapy, we selected a group of patients not treated by surgery or radiotherapy, and without any degree of hypopituitarism caused by the adenoma and/or its treatment: patients with microprolactinomas.

Furthermore, quality of life assessment had not been performed in patients with prolactinomas, whereas prolactinomas, and especially microprolactinomas, are the most prevalent pituitary adenomas (41;42). Therefore, in **chapter 4**, we assessed quality of life in 55 consecutive female patients with microprolactinomas treated currently or previously with dopamine agonists, and compared these results with 183 female control subjects with an equal distribution of age.

Anxiety and depression scores measured by the HADS were increased in patients with microprolactinomas compared to control subjects for all subscales. Patients also had higher scores for fatigue for all, but one, subscales measured by MFI-20. Compared to control subjects, quality of life was also reduced according to certain subscales of the SF-36 (social functioning, role limitations due to physical problems) and NHP (energy, emotional reaction, social isolation). Independent predictors of quality of life were reproductive status, and anxiety and depression according to the HADS. The use of dopamine agonists and current prolactin levels did not influence the scores on the questionnaires.

The present data indicate that female patients with microprolactinomas experience impaired quality of life, most likely in mental functioning, due to increased anxiety and depression. The cross-sectional study design did not permit to implicate causal mechanisms in the identified association of emotional impairment in patients with prolactinomas. One could only hypothesize on the influences of high levels of prolactin, or the effects of dopamine agonists on certain brain structures involved in the limbic system. Sobrinho has described the emotional aspects of hyperprolactinemia and the induced neural changes by prolactin (43). Prolactin modulates the activity of dopamine and density of dopamine receptors. Hyperprolactinemia increases hypothalamic dopaminergic tone, and this is termed the "short loop feedback". Moreover, the dopaminergic system is not limited to the hypothalamus, but widely spread in the brain. Most extensively studied are the mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular pathways (44;45). They are involved in emotion, feelings of reward and desire, cognition, motivation, locomotion, and inhibition of prolactin. Tuberoinfundibular dopaminergic neurons have a predominant role in the control of pituitary prolactin release, and their activity is higher in physiological increase of prolactin levels. In prolactinomas, the dopaminergic neurons become refractory to the autonomous elevated prolactin levels. Dopamine agonists activate the D2 dopamine receptor on lactotroph cells, thereby inhibiting prolactin release and suppressing prolactin gene expression. Subsequently, prolactin levels decrease, and as a consequence results in a lower activity of tuberoinfundibular dopaminergic neurons. Activity of dopaminergic neurons of mesolimbic system affects emotion, and feelings of reward and desire. The influence of dopamine agonist therapy on this dopaminergic system can only be assumed, and is not based on neurobiological or clinical evidence.

The questionnaires used were not disease-specific, *i.e.* they are developed to measure general physical, social, and psychological health aspects and not to measure quality of life in patients with prolactinomas. Therefore, disease-specific questions were not included in this analysis. Disease-specific questions in female patients with prolactinomas should be questions

related to the effects of hyperprolactinemia, and the use of dopamine agonists. Questions concerning hyperprolactinemia are questions about hypogonadotropic hypogonadism, including (in)fertility, amenorrhea, and libido. Questions related to dopamine agonist use should emphasize the burden to take medicine, compliance, and side-effects. Specific questionnaires for hypogonadism and drug application do exist, and could provide additional information and understanding of the decreased quality of life in patients with prolactinomas. However, we used four validated questionnaires regarding different aspects of quality of life, increasingly used in pituitary adenomas, including in patients treated for acromegaly, Cushing's disease and nonfunctioning macroadenoma in our center.

In conclusion, quality of life, and especially emotional well-being, is impaired in female patients with microprolactinomas compared to control subjects. Attention of the clinician to the health-related aspects of anxiety and depression might improve emotional well-being. One might postulate a causal association of hyperprolactinemia or dopaminergic drugs in specific limbic structures. However, these hypotheses need to be supported by future studies.

In **chapter 5**, we compared quality of life parameters between patients with different pituitary adenomas during long-term follow-up.

Pituitary adenomas do not only differ with respect to excessive hormone secretion (*e.g.* acromegaly, Cushing's disease, and prolactinoma), treatment modalities, and pituitary insufficiencies, but also in age and gender distributions. In this respect, age and gender are very important confounders in the comparison of quality of life parameters between patients with different pituitary adenomas. Therefore, we corrected for these confounding factors by age- and gender-specific standard deviation scores (Z-scores) of all quality of life subscales.

Patients were evaluated during long-term biochemical cure of acromegaly (n=118), Cushing's disease (n=58), during long-term follow-up of prolactinomas (n=128), or nonfunctioning macroadenomas (n=99).

In acromegaly, excessive growth hormone and IGF-1 levels cause gradual changes in facial and acral appearance, as well as in function of several internal tissues. Moreover, the somatotropic system interacts with cognition, mood and well-being. After successful treatment of the growth hormone excess, soft tissue swelling diminishes, and symptoms such as perspiration and paresthesias decrease. Other acromegalic features persist due to irreversible changes, for instance in bone and cartilage, causing serious arthropathy with invalidating complaints. Medical or surgical treatment alone is able to reach decrease excessive growth hormone and IGF-1 levels in only 50-70%. In the remaining patients, combinations of different treatments modalities are capable of long-term biochemical cure in almost all patients. Biermasz *et al*. showed that quality of life in patients with long-term biochemical cure of acromegaly is considerably decreased compared to control subjects (38). Furthermore, patients treated with radiotherapy had significantly worse general health and fatigue scores. Even patients cured after surgery had reduced quality of life, reflecting irreversible effects of previously active acromegaly.

In Cushing's disease, transsphenoidal surgery cures only two-thirds of the patients. Therefore, in the remaining patients treatment modalities such as radiotherapy and/or bilateral adrenalectomy are required to normalize cortisol levels. However, supraphysiological cortisol exposure induces temporary or permanent physical impairments, such as obesity, hypertension, diabetes mellitus, osteoporosis, and cardio-vascular disease. Furthermore, recovery of these impairments is often incomplete or very slow. In addition, hypercortisolism has been associated with reduced hippocampal volume and deficits in hippocampus-dependent memory tasks in humans. Van Aken *et al*. showed that quality of life is decreased in patients with Cushing's disease compared to control subjects, and, moreover, hypopituitarism negatively affected quality of life in these patients (39).

In nonfunctioning macroadenomas, transsphenoidal surgery is indicated in the presence of visual field defects. In the absence of visual impairments, observation alone is a safe alternative in our opinion. After surgery control of macroadenomas is achieved in more than two-third of the patients during long-term follow-up with improvement of visual field defects and visual acuity in ~80% of the patients. Dekkers *et al*. showed a substantial impairment of quality of life in patients with nonfunctioning macroadenomas compared to control subjects (40). The presence of hypopituitarism was the most predominant predictor of decreased quality of life, although it was present in 93% of the patients.

The present study compared quality of life parameters between patients during long-term follow-up after treatment of different pituitary adenomas. The study showed a significant decrease in quality of life for all subscales of the four health-related questionnaires in all patients compared to 440 control subjects of comparable age and gender. Perceived quality of life assessed by the total quality of life Z-score was significant different between patient groups with different pituitary adenomas, and was especially decreased in patients treated for acromegaly compared to patients treated for nonfunctioning macroadenomas or prolactinomas, reflected by higher Z-score. Disease-specific differences in the Z-scores were negatively affected in patients with acromegaly compared to patients with nonfunctioning macroadenomas and prolactinomas for the subscales physical ability and physical functioning according to NHP and SF-36, respectively. Patients treated for acromegaly perceived increased bodily pain compared to patients treated for nonfunctioning macroadenomas (SF-36). The Z-scores for physical functioning differ significantly between patients treated for Cushing's disease and for nonfunctioning macroadenomas, with the greatest impairment in patients with Cushing's disease. In addition, anxiety is increased in patients previously treated for Cushing's disease.

Persisting physical and psychological impairments affects quality of life in all patients with pituitary adenomas, despite long-term biochemical cure. Female gender and hypopituitarism were associated with a worse quality of life. Patients with acromegaly have the largest perceived decrease in quality of life, especially due to impairments in physical performance and increased bodily pain. This finding might be related to the irreversible changes in joints caused by previous growth hormone excess. One might expect a more severe decreased quality of life

in patients treated for Cushing's disease compared to patients treated for acromegaly. Hypercortisolism is associated with partial irreversible reduced hippocampal volume, psychiatric and psychological disturbances, and persistent physical changes.

Clinical implications. Patients with pituitary adenomas have impaired self-reported quality of life despite long-term biochemical cure and appropriate replacement therapies. Moreover, manifestations of reduced quality of life can not readily be assessed by clinical observations or biochemical measurements of simple plasma parameters. This makes it difficult to document to any extend this important issue in the out-patient clinic, whereas failure to recognize this association may overlook the impact of the disease on the life of the patient, and adversely affect patient-doctor relationships. Treatment should not only be aimed at biochemical cure and follow-up of physical manifestations, but should also be emphasized on improvement of self-perceived social, psychological, and emotional well-being. Most importantly, the patients should be appropriately informed of these long-term consequences of pituitary adenomas.

Malignant prolactinoma

In general, pituitary adenomas are benign diseases, without any propensity to metastasize, even though they may be in some circumstances locally invasive. However, rarely, patients present with malignant transformation of pituitary adenomas. In **chapter 6**, we describe the presentation, clinical course, and histopathological characteristics of a patient with the rare manifestation of a malignant prolactinoma. The patient presented initial with diplopia, ptosis of the right eye, and a nerve abducens palsy. During medical therapy with several kinds of dopamine agonists after each other, prolactin levels increased, and imaging showed invasive growth of the macroadenoma. Craniotomy and additional radiotherapy resulted in decrease of prolactin levels. However, after 14 months prolactin levels started to rise again. An epidepride (dopamine D2 receptor) scintigraphy showed intracranial and extracranial (spinal) pathological accumulation. Spinal metastases were confirmed by histopathological examination of the tissue derived from laminectomy. Adjuvant therapy with 3 courses of radiotherapy could not prevent progression of the primary and metastatic lesions, and the patient died 5 years after the initial presentation.

A detailed analysis of all 47 cases reported in the literature and the present case report reveals several characteristics that distinguish a malignant prolactinoma from ordinary prolactinomas. First, the aggressive clinical course: presentation with symptoms of cranial nerve compression, an invasive adenoma on imaging, and the resistance of prolactinomas and prolactin levels to dopamine agonists. Second, the histopathological findings. In retrospect, histopathological examination of the tissues derived from the craniotomy and laminectomy of the present case revealed high proliferative index, with a Ki-67 labeling index of 10-15%. Histopathological parameters associated with high proliferative tissue and aggressive behaviour of tissue are cellular atypia, nuclear pleomorphism, more than two mitotic figures per ten high-powered field, Ki-67 index of 3% or more, positive p53 immunoreactivity, and invasion (46;47). Although

these parameters are indicative for an aggressive type of adenoma, they are not conclusive for the diagnosis malignant prolactinoma. Such a diagnosis can, unfortunately, only be confirmed until the third characteristic occurs: metastasis.

Malignant prolactinoma has a poor prognosis with mean survival of almost two years after metastasis are diagnosed, and with less than one-third of the patients being alive at the moment of publication. Furthermore, it seems that adjuvant therapy (surgery, radiotherapy, chemotherapy, octreotide, and/or dopamine agonists) are of little influence on the aggressive behaviour of the disease, though this is an observation derived from the present review and not at all evidence based.

Clinical implications. The development of resistance to dopamine agonists and/or growth of adenoma during treatment with dopaminergic drugs should alert the clinician. In this situation, the diagnosis malignant prolactinoma should be considered, and if tissue is available (for example derived from surgery to relieve optic nerve compression) specific histopathological examination should be preformed. Especially a high Ki-67 labeling index, p53 immunoreactivity, and high mitotic index are associated with atypical and aggressive behavior, and support the differential diagnosis of malignant prolactinoma. Additional total body imaging is warranted, although metastases are mostly discovered by focused imaging of complaints due to local compression of tumor mass.

CONCLUDING REMARKS

Dopamine agonists were the first effective medical treatment for pituitary adenomas. The general efficacy of this treatment was associated with the general notion of doctors that the treatment of prolactinomas is straightforward and merely consists of prescribing dopamine agonists. Consequently, these patients are treated by different sorts of specialists including internists, endocrinologists, pediatricians, and gynecologists. However, the studies documented in this thesis prove that the treatment of this disease is not simple in all respects.

Even in the case of microprolactinomas, with an adequate response to dopamine agonists, patients may be dissatisfied with the treatment of the doctor, because they suffer from a considerable decrease in perceived quality of life parameters. This dissatisfaction may adversely affect patient-doctor relationships.

Long-term treatment of macroprolactinomas is not straightforward in case there is resistance or intolerance to dopamine agonists. In these situations, therapy may be switched to another dopamine agonist. In case this switch is unsuccessful, surgical treatment is a second line option. In individual cases a choice may be made for additional postoperative radiotherapy. The second and third line treatments are associated with a much higher incidence of hypopituitarism, and therefore the choice for these treatment modalities may further impair quality of life.

Long-term treatment of prolactinomas is associated with an increased prevalence of mild tricuspid regurgitation and calcification of the aortic valve in the absence of increased clinically relevant valve regurgitation. The clinical relevance of this observation is presently unclear, but this observation should not be taken too lightly. For instance, during long-term treatment of macroprolactinomas only 22% of the patients were cured, whereas the other patients required prolongation of dopamine agonist therapy, which ultimately may potentially adversely affect valvular functions.

Finally, in extremely rare situations the clinical course of a prolactinoma may be more complicated and aggressive which should alert the physician on the possibility of the existence of a malignant prolactinoma.

The studies presented in the current thesis indicate that dedicated care is required for all patients with prolactinomas.

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Chapter 8

SAMENVATTING

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Prolactinomen zijn hypofyse adenomen met een autonome produktie van prolactine, uitgaande van lactotrope cellen. De hypofyse is een klein orgaan, dat zich onderaan de hersenen bevindt, en vele soorten hormonen aanmaakt en afgeeft. Prolactine wordt normaliter aan het einde van en na de zwangerschap in grote hoeveelheden gemaakt om na de zwangerschap de borstvoeding op gang te laten komen. Mannen maken ook prolactine, maar de functie van prolactine bij hen is niet helemaal duidelijk. Hyperprolactinemie (*i.e.* een te hoog prolactine gehalte) veroorzaakt symptomen of verschijnselen zoals infertiliteit, menstruatiestoornissen, verminderd libido, of melkuitvloed uit de borsten. Daarnaast kunnen ook verschijnselen ontstaan ten gevolge van de massawerking van het adenoom, zoals gezichtsvelddefecten en verminderde produktie van hormonen door de hypofyse. Prolactinomen worden ingedeeld naar grootte: een microprolactinoom is kleiner dan 1 cm in doorsnede, een macroprolactinoom is groter dan of gelijk aan 1 cm in doorsnede, en een "giant" prolactinoom is groter dan 4 cm in doorsnede. De behandeling van een prolactinoom is gericht op normalisering van het prolactine gehalte en afname van de grootte van het adenoom in de hypofyse. Dit betekent langdurige controle en follow-up. Voorts hebben patiënten met een prolactinoom veel klachten op grond van een verminderde kwaliteit van leven, met name ten gevolge van angst en depressieve gevoelens.

Dopamine agonisten zijn sinds de jaren zeventig van de vorige eeuw de eerste keus in de behandeling van prolactinoom. Dopamine agonisten, en met name cabergoline, hebben bewezen effectief te zijn in het normaliseren van het prolactine gehalte en afname van de grootte van het adenoom. Echter, onlangs bleek dat de aan ergotamine verwante dopamine agonist cabergoline geassocieerd is met het ontstaan van hartklepafwijkingen bij patiënten met de ziekte van Parkinson. Derhalve zijn er vragen gerezen over de veiligheid van dit effectieve geneesmiddel.

In dit proefschrift worden diverse aspecten van de behandeling en lange termijn follow-up van patiënten met prolactinomen belicht.

Lange termijn uitkomsten van patiënten met macroprolactinoom, die in eerste instantie behandeld zijn met dopamine agonisten

De behandeling van macroprolactinomen bestaat primair uit dopamine agonisten, welke de prolactine secretie remmen en tumorgrootte verkleinen (1-13). Intolerantie, met klachten zoals misselijkheid en orthostatische hypotensie, belemmeren bij sommige patiënten de voortzetting van de behandeling met dopamine agonisten. Derhalve zijn andere behandelmodaliteiten nodig, zoals transsphenoidale chirurgie en/of radiotherapie. De korte termijn biochemische en radiologische response van micro- en macroprolactinomen op dopamine agonisten is uitvoerig gedocumenteerd (1-13). Opmerkelijk genoeg zijn er slechts 4 studies, die de lange termijn uitkomsten van de behandeling met dopamine agonisten in patiënten met macroprolactinomen hebben gerapporteerd (14-17). Echter, deze studies zijn incompleet betreffende

diverse uitkomsten, zoals hypofyse uitval, radiologische recidief, biochemische remissie, en omvatten slechts kleine aantallen patiënten. Er zijn derhalve nog diverse onduidelijkheden met betrekking tot de lange termijn uitkomsten van medicamenteuze behandeling van patiënten met macroprolactinoom, die primair behandeld zijn met dopamine agonisten. In **hoofdstuk 2** worden de lange termijn uitkomsten van endocriene en radiologische parameters beschreven van patiënten initieel behandeld met dopamine agonisten voor een macroprolactinoom.

Tweeënzeventig opeenvolgende mannen en vrouwen met een macroprolactinoom werden in eerste instantie behandeld met dopamine agonisten. Bij 65% van deze patiënten waren dopamine agonisten alleen afdoende om de hyperprolactinemie en het hypofyse adenoom te behandelen. Aanvullende behandeling in de vorm van transsphenoidale chirurgie was nodig bij 35% van de patiënten. Dopamine resistentie en intolerantie waren de voornaamste reden om te opereren. Postoperatieve radiotherapie was nodig bij 18% van de patiënten. Normalisatie van het prolactine gehalte ontstond uiteindelijke bij 85% van de patiënten, hoewel volledige biochemische remissie (*i.e.* normaal prolactine gehalte na het staken van de dopamine agonisten) slechts bestond bij 22% van alle patiënten na langdurige follow-up, en slechts bij 33% van de patiënten die naast de dopamine agonisten tevens behandeld zijn met transsphenoidale chirurgie en/of radiotherapie. Hypofyse uitval trad op bij 39% van alle patiënten. Additionele behandelingen deed het percentage hypofyse uitval oplopen van 21% bij patiënten die enkel behandeld werden met dopamine agonisten, tot 67% bij patiënten die behandeld waren met transsphenoidale chirurgie, en tot 77% bij patiënten die tevens behandeld waren met postoperatieve radiotherapie. Radiologische beeldvorming liet tumor groei zien bij 7% van de patiënten, terwijl een recidief van het adenoom bij 4% van de patiënten optrad. Bij 57% van de patiënten trad een afname van het adenoom op.

Deze studie bevestigt de effectiviteit van dopamine agonisten bij macroprolactinomen wat betreft de controle van de hyperprolactinemie en tumorgrootte op korte termijn van vorige studies (14-19). Hamilton *et al.* rapporteerde remissie bij 27% van de 45 patiënten met een macroprolactinoom behandeld met chirurgie in verband met resistentie voor dopamine agonisten (18). Losa *et al.* documenteerde remissie bij ~45% van 61 patiënten met een macroprolactinoom behandeld met chirurgie (19). In diverse andere studies was chirurgische behandeling nodig bij 14-38% van de patiënten wegens falen van of resistentie voor dopamine agonisten (14-17), met een remissie van 8%, gerapporteerd door slechts 1 studie (14). Berinder *et al.* en Wu *et al.* presenteerden data betreffende aanvullende behandeling met radiotherapie, welke in respectievelijk 14 en 50% van de patiënten nodig was (16;17). Hieruit blijkt al dat een relevant deel van de patiënten met een macroprolactinoom aanvullende behandeling nodig heeft.

Lange termijn data betreffende hypofyse uitval na diverse behandelmodaliteiten zijn schaars. Enkel Chattopadhyay en zijn collega's hebben de resultaten na behandeling met bromocriptine bij alle patiënten en chirurgie in eenderde van de patiënten beschreven (15). Zij vonden dat 55% van de 29 patiënten met een macroprolactinomen uitval van een van de hypofyse assen had na 2,6 jaar follow-up. Het optreden van een recidief adenoom trad slechts

zelden op. Bij 14 patiënten behandeld met bromocriptine en/of chirurgie en aanvullende radiotherapie voor een "giant" prolactinoom kreeg geen van de patiënten een recidief tijdens een mediane follow-up duur van 9 jaar (17).

Onze studie heeft enkele beperkingen welke inherent zijn aan de retrospectieve opzet van de studie. In de initiële fase van de studie periode was slechts bromocriptine beschikbaar als enige dopamine agonist voor de behandeling van prolactinomen. Bromocriptine heeft, echter, vergeleken met bijvoorbeeld cabergoline, enkele nadelen, zoals een korte halfwaarde tijd waardoor het meerdere keren per dag dient te worden ingenomen, en het frequente optreden van bijwerkingen. De therapietrouw van patiënten behandeld met bromocriptine is dientengevolge minder ten op zichten van patiënten behandeld met cabergoline. Dit kan leiden tot recidief van de hyperprolactinemie na het (vroegtijdig) staken van bromocriptine, en maakt aanvullende behandeling met bijvoorbeeld transsphenoidale chirurgie noodzakelijk. Het is zeer waarschijnlijk dat de resultaten beter zouden zijn geweest als alle patiënten behandeld waren geweest met cabergoline, wat effectiever is en minder bijwerkingen geeft (5;6;20). Echter, ook cabergoline gaat gepaard met optreden van falen van de behandeling van macroprolactinomen. Dit treedt op bij ongeveer 10-20% van de patiënten (21;22). Alhoewel niet alle patiënten cabergoline gebruikten, blijft de huidige studie een unieke beschrijving van de lange termijn follow-up van patiënten met een macroprolactinoom initieel behandeld met dopamine agonisten, en van de effecten op lange termijn op endocriene en radiologische uitkomstmaten.

Binnen de afdeling Endocrinologie van het Leiden Universitair Medisch Centrum zijn alle patiënten met een hypofyse adenoom geanalyseerd wat betreft de lange termijn follow-up na diverse soorten behandelingen (23;24). Een overzicht van de gegevens in deze studies, betreffende patiënten met acromegalie, ziekte van Cushing, en niet-functionerend hypofyse adenomen, en van de huidige studie over macroprolactinomen wordt gegeven in tabel 1. Patiënten gediagnosticeerd met acromegalie, ziekte van Cushing, of niet-functionerend hypofyse adenomen werden allen primair behandeld middels transsphenoidale chirurgie. Postoperatieve radiotherapie werd toegepast om recidieven te voorkomen, persisterende ziekte te behandelen, of om recidieven te behandelen. Primair medicamenteuze behandeling met somatostatine analogen kan tegenwoordig overwogen worden in de behandeling van patiënten met acromegalie, en is succesvol bij ongeveer 60% van de patiënten (25). Patiënten met een prolactinoom worden, in tegenstelling tot patiënten met andere hypofyse adenomen, primair behandeld met dopamine agonisten. Behandeling middels transsphenoidale chirurgie en postoperatieve radiotherapie worden gereserveerd als respectievelijk secundaire en tertiaire behandelingsstrategieën. Er zijn indrukwekkende en belangrijke verschillen in endocriene en radiologische uitkomsten op de lange termijn tussen de verschillende hypofyse adenomen. Patiënten met een niet-functionerend hypofyse adenoom hebben vaker hypofyse uitval (93%) vergeleken met patiënten met acromegalie (32%), terwijl ongeveer een gelijke proportie van de patiënten bestraald is geweest (respectievelijk 36 en 34%). Dit zou verklaard kunnen

Tabel 1. Lange termijn follow-up van verschillende hypofyse adenomen na behandeling met diverse modaliteiten in een centrum

	Acromegalie	Ziekte van Cushing	Niet-functionerend macroadenoom	Macro-prolactinoom
Aantal patiënten	164	74	174	72
Studie periode	1977-2002	1977-2005	1977-2005	1980-2004
M/V, *No.*	91/73	18/56	98/76	33/39
Leeftijd*, *jr*	47	39	55	39
Follow-up duur, *jr*	12	13	9	10
Behandeling				
Medicatie†, *%*	13	-	-	100
Chirurgie, *%*	100	100	100	35
Radiotherapie, *%*	34	19	36	18
Uitkomst				
Hypofyse uitval, *%*	32	44	93	39
Recidief, *%*	9	16	16	4
Remissie, *%*	88	93	84	22
SMR	1.33	2.39	1.24	niet beschikbaar

Data zijn uitgedrukt als gemiddelde, tenzij anders vermeld. Definitie van hypofyse uitval: uitval van 1 of meer as. Definitie van recidief: biochemisch recidief met stijging van het groeihormoon boven 2,5 µg/L (5 mU/L) in patiënten met acromegalie; biochemisch recidief van hypercortisolisme in patiënten met ziekte van Cushing (*i.e.* onvoldoende suppressie van plasma cortisol na 1 mg orale dexamethason (cortisol > 100 nmol/L de volgende ochtend) en/of abnormale 24-uurs urine vrije cortisol excretie in twee opeenvolgende monsters); radiologisch recidief met het ontstaan van een tumor massa in de afwezigheid van tumor massa op een voorafgaande MRI in patiënten met niet-functionerend macroadenoom en macroprolactinoom. Definitie van remissie: groeihormoon waarde < 2,5 µg/L in patiënten met acromegalie; normale suppressie na 1 mg orale dexamethason (cortisol < 100 nmol/L de volgende ochtend) en normale 24-uurs urine vrije cortisol excretie in twee opeenvolgende monsters in patiënten met de ziekte van Cushing; afwezigheid van recidief in niet-functionerend macroadenoom; normale prolactine waarden na staken van dopamine agonist in macroprolactinomen. M, man; V, vrouw; jr, jaar; SMR, standardized mortality ratio.
* Gemiddelde leeftijd tijdens operatie bij patiënten met acromegalie, ziekte van Cushing, en niet-functionerende macroadenomen; gemiddelde leeftijd bij diagnose bij patiënten met macroprolactinomen.
† Medicatie: behandeling met octreotide bij patiënten met acromegalie; behandeling met dopamine agonisten bij patiënten met macroprolactinomen.
Referenties: (23;24)

worden door de pre-operatieve tumor grootte. Patiënten met een niet-functionerend hypofyse adenoom hadden in 30% van de gevallen een invasief macroadenoom, terwijl slechts 21% van de patiënten met acromegalie een invasief macroadenoom had. Bij 85% van de patiënten met de ziekte van Cushing was er sprake van een microadenoom, waarbij slechts bij 44% van de patiënten uitval van de hypofyse assen optrad. Een andere verklaring zou gelegen kunnen zijn in de hoeveelheid patiënten die hypofyse uitval hadden voor de behandeling: bij 85% van de patiënten met een niet-functionerend hypofyse adenoom, vergeleken met respectievelijk 3% en 6% bij patiënten met acromegalie of macroprolactinoom.

Een andere opmerkelijke uitkomst is het verschil in remissie tussen de diverse hypofyse adenomen. Patiënten met acromegalie, ziekte van Cushing, of een niet-functionerend hypofyse adenoom hebben allen een vergelijkbare uitkomst wat betreft remissie, gelegen tussen de 84 en 93% na behandeling met diverse modaliteiten. Echter, bij patiënten met een macroprolactinoom wordt na langdurige follow-up een remissie (*i.e.* normaal prolactine gehalte na staken van dopamine agonisten) bij slechts 22% van de patiënten bereikt, waarbij overigens wel 85% van de patiënten een normaal prolactine gehalte heeft tijdens langdurige follow-up met of zonder dopamine agonisten. Blijkbaar zijn patiënten met macroprolactinomen initieel behandeld met dopamine agonisten niet vergelijkbaar met patiënten met andere hypofyse adenomen wat betreft remissie. De lange termijn gevolgen van behandeling van macroprolactinomen zijn dientengevolge beduidend slechter dan die van de andere hypofyse adenomen. Dit wordt onvoldoende gerealiseerd door de meeste artsen die macroprolactinomen behandelen.

Klinische implicaties. Dopamine agonisten zijn eerste keus van behandeling van macroprolactinomen, resulterend in normalisering van het prolactine gehalte bij 85%, verkleining van de tumor bij 57%, en remissie bij slechts 22% van de patiënten op de lange termijn. Additionele behandeling met transsphenoidale chirurgie blijft nodig voor patiënten met resistentie of intolerantie voor dopamine agonisten. Gezien de hoge prevalentie van het optreden van hypofyse uitval na radiotherapie, dient deze behandeling zeer zorgvuldig te worden overwogen, en is voornamelijk geïndiceerd voor de behandeling van tumor massa, dan voor het bereiken van daling van het prolactine gehalte.

Prevalentie van hartklepafwijkingen bij patiënten die vanwege een prolactinoom behandeld zijn met dopamine agonisten

De aan ergotamine verwante dopamine agonisten cabergoline en pergolide zijn potente agonisten van de 5-HT_{2b}-receptoren met een hoge bindingsaffiniteit voor deze serotonine receptoren, vergeleken met bromocriptine en lisuride. Stimulatie van de 5-HT_{2B}-receptoren, welke in hoge mate aanwezig zijn op hartkleppen, activeert de mitogenese van fibroblasten, leidend tot fibrose en verdikking van hartkleppen. Uiteindelijk leidt dit tot ernstige klep regurgitatie met de noodzaak tot operatieve klepvervanging. Diverse studies hebben een verhoogde prevalentie van klinisch relevante klep regurgitaties tijdens of na de behandeling met cabergoline of pergolide bij patiënten met ziekte van Parkinson laten zien (26-32). De afwijkingen aan de hartkleppen bij deze patiënten komen overeen met de afwijkingen gezien bij patiënten behandeld met vermagerings- of anti-migraine medicatie, en patiënten met het serotonine secernerende carcinoid syndroom (33-37). Echter, er zijn geen gegevens bekend betreffende het gebruik van cabergoline in patiënten behandeld voor prolactinoom. Cabergoline is bij de behandeling voor prolactinoom lager gedoseerd vergeleken met de behandeling voor ziekte van Parkinson, maar wordt wel veel langer voorgeschreven bij prolactinomen. Voorts verschillen patiënten behandeld voor een prolactinoom van patiënten behandeld voor de ziekte van Parkinson wat betreft de verdeling van geslacht en leeftijd. Er is dus onduidelijkheid over de

veiligheid van cabergoline bij de behandeling van prolactinoom, en opheldering is derhalve zeer gewenst.

In **hoofdstuk 3** beschrijven we de uitkomsten van echocardiografische evaluatie van de hartkleppen bij 78 patiënten, die langdurig met dopamine agonisten worden behandeld voor een prolactinoom. Middels dit onderzoek hebben we de prevalentie van klep regurgitatie en de klepmorfologie vastgesteld. We hebben deze uitkomsten vergeleken met 78 controle personen, overeenkomend wat betreft leeftijd, geslacht, lichaamsoppervlakte, en systolische functie van de linker ventrikel. De data van deze controle personen zijn afkomstig uit een database met echografie gegevens. De patiënten behandeld voor een prolactinoom konden worden verdeeld in twee groepen: 47 patiënten die cabergoline gebruikte (gemiddelde duur 5,2 jaar, gemiddelde cumulatieve dosis van 363 mg) en 31 patiënten die geen cabergoline gebruikt hadden (*i.e.* zij waren behandeld met bromocriptine, terguride, quinagolide, of geen dopamine agonisten). De uitkomsten van de echocardiografische analyse werden vergeleken tussen beide groepen om na te gaan of er wellicht medicatiespecifieke aspecten van invloed op de uitkomsten waren.

Er was bij de patiënten behandeld voor prolactinoom geen hogere prevalentie van klinisch relevante klep regurgitatie vergeleken met controle personen. Echter, er was wel sprake van een verhoogde prevalentie van milde tricuspidalis regurgitatie en calcificaties van de aorta klep bij patiënten behandeld met prolactinomen, vergeleken met controle personen.

Het voornaamste probleem van deze studie was dat een groot deel van patiënten die behandeld werden met cabergoline, in het verleden ook behandeld waren met andere dopamine agonisten. Studies met een beter onderscheid tussen patiënten die cabergoline gebruikt hebben en patiënten die geen cabergoline gebruikt hebben zijn daarom wenselijk. Bovendien is het noodzakelijk te bestuderen wat de implicaties op klepfuncties en klepmorfologie zijn bij een langere behandelingsduur.

Twee patiënten, behandeld met cabergoline, hadden bij toeval een bicuspide aortaklep. Een van deze patiënten had een ernstige aortaklep regurgitatie, waardoor er een indicatie was voor hartklepchirurgie. Er werd bij deze patiënt een aortawortel vervanging met plaatsing van een aorta bioklep prothese verricht. De thoraxchirurg constateerde tijdens de operatie macroscopische veranderingen aan de aortaklepbladen, bestaande uit calcificaties en verdikking. Pathologisch anatomisch onderzoek van de aorta ascendens toonde geringe fibrotische verdikkingen van de intima. Deze 46-jarige mannelijke patiënt werd gedurende 8,5 jaar behandeld met cabergoline, met een cumulatieve dosis van 362 mg (gemiddelde dosis per week van 0,8 mg). Hij was 13 jaar voor de echografie gediagnosticeerd met macroprolactinoom, en in eerste instantie behandeld met quinagolide. Hij rookte, had een BMI van 23 kg/m2, zijn bloeddruk was 111/69 mmHg, en hij had een normaal prolactine gehalte en normale lipiden waarden op het moment van de echocardiografie.

Het is vooralsnog onduidelijk wat de ***klinische implicaties*** zijn van de verhoogde prevalentie van milde tricuspidalis regurgitatie en van calcificaties van de aortaklep voor de dagelijkse

praktijk. Cabergoline lijkt vooralsnog veilig bij de behandeling van patiënten met een prolactinoom, en er lijkt, met de huidige onderzoeksgegevens, geen indicatie te zijn om cabergoline te vervangen door een andere dopamine agonist. Echter, het is niet uitgesloten dat langduriger gebruik van lage doseringen cabergoline fibrotische veranderingen van de hartkleppen kan induceren, waarvan de momenteel gevonden verdikkingen en verkalkingen een vroeg teken zouden kunnen zijn. Aanvullende studies bij meer patiënten met langer gebruik van cabergoline zijn nodig om hier helderheid over te verkrijgen.

Kwaliteit van leven bij patiënten behandeld voor een prolactinoom en andere hypofyse adenomen

De evaluatie van gezondheidsgerelateerde kwaliteit van leven heeft recentelijk veel aandacht gekregen. De impact van endocriene ziekten op psychologisch en sociaal welzijn is veel moeilijker te documenteren, dan fysieke klachten en symptomen. Alhoewel chronische ziekten in het algemeen geassocieerd zijn met een beperking in de kwaliteit van leven, onderscheiden hypofyse adenomen zich van andere aandoeningen door de directe invloeden van hormonale overproduktie of deficiënties op het limbische-hypothalame systeem. Subtiele veranderingen van psychologisch of sociaal welzijn worden in de dagelijkse praktijk door de dokter over het hoofd gezien, hoewel ze een enorme impact hebben op het leven van de patiënt. Dit heeft op zich weer invloed op de arts-patiënt relatie, met name als deze beperkingen door de arts niet in het juiste perspectief worden geschat. Parameters voor de kwaliteit van leven werden derhalve geëvalueerd in grote cohorten van opeenvolgende patiënten behandeld voor een hypofyse adenoom in het Leiden Universitair Medisch Centrum.

Vier gevalideerde, gezondheidsgerelateerde kwaliteit van leven vragenlijsten werden gebruikt om de kwaliteit van leven te evalueren in alle patiënten met een hypofyse adenoom: Short-Form-36 (SF-36), Nottingham Health Profile (NHP), Multidimensional Fatigue Inventory (MFI-20), en de Hospital Anxiety and Depression Scale (HADS). De uitkomsten van de patiënten werden vergeleken met de resultaten van een controle groep, met overeenkomstige spreiding van geslacht en leeftijd, afkomstig uit hetzelfde geografische gebied, en met een vergelijkbare sociaal-economische achtergrond. Het doel van deze studies, beschreven in **hoofdstuk 4 en 5**, was om de verschillende fysieke en psychologische aspecten van de kwaliteit van leven te evalueren bij patiënten met een prolactinoom en om te bestuderen of er ziektespecifieke beperkingen in kwaliteit van leven zijn bij patiënten met verschillende hypofyse adenomen.

We includeerden patiënten met een langdurige curatie dan wel biochemische controle van acromegalie, de ziekte van Cushing, als ook patiënten behandeld voor niet-functionerend hypofyse macroadenomen. Onze onderzoeksgroep heeft in het verleden gedocumenteerd dat de kwaliteit van leven parameters beperkt zijn bij deze patiënten vergeleken met controle personen. Irreversibele effecten van hormonale overproduktie, radiotherapie en hypofyse uitval bleken een negatief effect te hebben op het fysieke en psychologische welzijn bij patiënten met deze aandoeningen (38-40). Omdat we geïnteresseerd waren in de gevolgen van de behandeling en langdurige follow-up van een hypofyse adenoom bij patiënten zonder de verstorende

invloeden van chirurgie en radiotherapie, hebben we een groep patiënten geselecteerd die niet behandeld is met chirurgie of radiotherapie, en geen hypofyse uitval heeft: patiënten met microprolactinoom. Tevens is de kwaliteit van leven in patiënten met een prolactinoom niet eerder geëvalueerd, alhoewel prolactinomen, en met name microprolactinomen, de meest prevalente hypofyse adenomen zijn (41;42).

In **hoofdstuk 4** wordt de evaluatie van kwaliteit van leven bij 55 opeenvolgende vrouwelijke patiënten met een microprolactinoom die ten tijde van de studie of in het verleden behandeld zijn met dopamine agonisten vergeleken met de resultaten van 183 vrouwelijk controle personen met een vergelijkbare leeftijd, weergegeven.

Angst en depressie scores gemeten met de HADS waren verhoogd bij patiënten met een microprolactinoom vergeleken met controle personen voor alle subschalen. Patiënten hadden tevens een hogere score voor moeheid voor alle subschalen, behoudens een, gemeten met de MFI-20. Vergeleken met controle personen was de kwaliteit van leven verminderd volgens bepaalde subschalen van de SF-36 (sociaal functioneren, rolbeperkingen t.g.v. fysieke problemen) en de NHP (energie, emotionele reactie, sociale isolatie). Onafhankelijke voorspellers van kwaliteit van leven waren de aan- of afwezigheid van een regelmatige menstruatie, en angst en depressie volgens de HADS. Het al dan niet gebruiken van dopamine agonisten evenals het prolactine gehalte gemeten ten tijde van de studie, hadden geen invloed op de scores van kwaliteit van leven.

De huidige data geven aan dat vrouwen, behandeld voor een prolactinoom, beperkingen in hun kwaliteit van leven ervaren, voornamelijk in mentaal functioneren ten gevolge verhoogde angst en depressieve gevoelens. De cross-sectionele studie opzet staat het niet toe om onderliggende causale mechanismen te duiden die ten grondslag liggen aan de emotionele beperkingen bij deze patiënten. Men kan enkele hypotheses postuleren over de invloeden van hoge prolactine gehaltes of de effecten van dopamine agonisten op bepaalde structuren in het centrale zenuwstelsel betrokken bij het limbische systeem. Sobrinho heeft de emotionele aspecten van hyperprolactinemie en de neurale veranderingen door prolactine beschreven (43). Prolactine moduleert de activiteit van dopamine en de densiteit van dopamine receptoren. Hyperprolactinemie verhoogt de inhiberende dopaminerge actie vanuit de hypothalamus, welke ook wel de “short loop feedback” genoemd wordt. Het dopaminerge systeem is niet beperkt tot de hypothalamus, maar is wijd verspreid door de hersenen. De mesolimbische, mesocorticale, nigrostratiale en tuberoinfundibulaire systemen zijn het meest bestudeerd (44;45). Ze zijn betrokken bij emotie, gevoelens van waardering en verlangen, cognitie, motivatie, beweging, en remming van afgifte en produktie van prolactine. Tuberoinfundibulaire dopaminerge neuronen hebben een overheersende rol in de regulatie van hypofysaire prolactine afgifte, en hun activiteit is verhoogd in fysiologische omstandigheden met verhoogd prolactine gehalte. De dopaminerge neuronen worden resistent voor de autonoom verhoogde prolactine gehaltes bij prolactinomen. Dopamine agonisten activeren de dopamine D2 receptor op lactotrope cellen, waardoor prolactine afgifte wordt geremd en genexpressie van het prolactine gen wordt

onderdrukt. Als gevolg hiervan daalt het prolactine gehalte, met vervolgens weer een lagere activiteit van de tuberoinfundibulaire dopaminerge neuronen. De activiteit van dopaminerge neuronen van het meso-limbische systeem beïnvloedt emotie, en gevoelens van waardering en verlangen. De invloed van dopamine agonisten op dit dopaminerge systeem kan enkel worden verondersteld, en is niet gebaseerd op neurobiologische of klinische bewijsvoering.

De vragenlijsten zijn ontwikkeld om algemene fysieke, sociale en psychologische gezondheidsgerelateerde aspecten te meten. Ziektespecifieke vragen over de gevolgen van een prolactinoom en de behandeling met dopamine agonisten werden dus niet betrokken in deze analyse. Vragen met betrekking tot de gevolgen van hyperprolactinemie hebben betrekking op de effecten van hypogonadotroop hypogonadisme, zoals ongewenste onvruchtbaarheid, menstruatiestoornissen, en verminderde libido. Vragen over de effecten van het gebruik van dopamine agonisten bevatten onderwerpen zoals de last van het gebruik van medicijnen, therapietrouw, en bijwerkingen. Er bestaan vragenlijsten over deze specifieke onderwerpen, welke aanvullende informatie zouden kunnen verschaffen over de onderliggende oorzaken van de verminderde kwaliteit in leven in patiënten met prolactinoom.

Samenvattend kunnen we stellen dat de kwaliteit van leven, en met name het emotionele welzijn, verminderd is bij vrouwelijke patiënten met een microprolactinoom vergeleken met controle personen. Behandelende artsen zouden meer rekening moeten houden met deze gezondheidsgerelateerde aspecten van angst en depressie. We kunnen slechts speculeren over de onderliggende mechanismen van de relatie tussen hyperprolactinemie en/of het gebruik van dopamine agonisten enerzijds en de effecten hiervan op de hersenen, die betrokken zijn bij de verminderde kwaliteit van leven, anderzijds.

In **hoofdstuk 5** worden de beperkingen in kwaliteit van leven vergeleken tussen patiënten die behandeld zijn voor verschillende hypofyse adenomen geëvalueerd.

Hypofyse adenomen verschillen niet alleen in specifieke hormonale excessieve produktie (*e.g.* acromegalie, ziekte van Cushing, en prolactinoom), behandelmodaliteiten en hypofyse uitval, maar ook in de verdeling van leeftijd en geslacht van de verschillende patiënten groepen. Leeftijd en geslacht op zich hebben een belangrijke invloed op kwaliteit van leven parameters. De vergelijking van de kwaliteit van leven tussen patiënten met verschillende hypofyse adenomen wordt derhalve niet alleen beïnvloed door de ziektes, maar ook door verschillen in leeftijd en geslacht. We hebben voor deze confounders gecorrigeerd door geslacht- en leeftijdspecifieke standaard deviatie scores (Z-scores) voor alle kwaliteit van leven subschalen vast te stellen.

De patiënten werden geëvalueerd na langdurige biochemische curatie van acromegalie (n=118), of van de ziekte van Cushing (n=58), of gedurende langdurige follow-up na behandeling van niet-functionerend hypofyse macroadenoom (n=99) of prolactinoom (n=128). Acromegalie ontstaat door een hypofyse adenoom die excessieve hoeveelheden groeihormoon produceert, waardoor geleidelijke veranderingen optreden van gezicht, handen en voeten en interne organen. Voorts heeft het groeihormoon invloed op cognitie, stemming, en welzijn. Na

een succesvolle behandeling van de autonome groeihormoon produktie neemt de zwelling van de weke delen vrij snel af, en verminderen de klachten van zweten en tintelingen. Echter, andere eigenschappen, zoals veranderingen aan bot en kraakbeen, persisteren en veroorzaken invaliderende klachten zoals ernstige gewrichtsklachten. Medische of chirurgische behandeling is weliswaar in staat om het groeihormoon te doen dalen bij 50-70% van de patiënten. Bij de overige patiënten, is een combinatiebehandeling in staat tot langdurige biochemische controle van groeihormoon exces bij vrijwel alle patiënten. Biermasz *et al.* hebben aangetoond dat de kwaliteit van leven behoorlijk beperkt is bij patiënten na langdurige biochemische controle van de ziekteactiviteit vergeleken met controle personen (38). Voorts bleek dat met name de patiënten behandeld met radiotherapie de slechtste algemene gezondheid en de meeste moeheidklachten hadden. Zelfs de patiënten die door chirurgische behandeling genezen zijn, hadden een verminderde kwaliteit van leven, wat aangeeft dat er irreversibele effecten zijn van de voorheen actieve ziekte acromegalie.

Tweederde van de patiënten met de ziekte van Cushing is genezen na een initiële behandeling met transsphenoidale chirurgie, waarbij de overige patiënten door middel van radiotherapie en/of bilaterale adrenalectomie als nog normalisatie van cortisol waarden krijgen. Echter, de blootstelling aan suprafysiologische cortisol waarden induceert tijdelijke of waarschijnlijk ook permanente gevolgen, zoals overgewicht, hypertensie, diabetes mellitus, osteoporose, en cardio-vasculaire aandoeningen. Het herstel van deze beperkingen na een operatie is incompleet en erg traag. Tevens is hypercortisolisme geassocieerd met een afname van volume van de hippocampus en beperkingen in hippocampus gerelateerde geheugentaken. Van Aken *et al.* hebben de verminderde kwaliteit van leven bij patiënten behandeld voor ziekte van Cushing ten opzichte van controle personen aangetoond, waarbij met name hypofyse uitval de kwaliteit van leven negatief beïnvloed heeft (39).

In ons ziekenhuis is de aanwezigheid van gezichtsvelddefecten bij patiënten met niet-functionerend hypofyse macroadenoom de belangrijkste indicatie voor transsphenoidale chirurgie. Als er geen gezichtsvelddefecten aanwezig zijn, is observatie naar onze mening een veilig alternatief voor operatie. Er is bij meer dan tweederde van de patiënten, geopereerd aan niet-functionerend hypofyse macroadenoom, adequate controle van de ziekte na langdurige follow-up, met verbetering van de gezichtsvelddefecten en gezichtsscherpte bij ongeveer 80% van de patiënten. Dekkers en collega's vonden een substantiële beperking van de kwaliteit van leven bij patiënten behandeld met transsphenoidale chirurgie voor een niet-functionerend hypofyse macroadenoom vergeleken met controle personen (40). De aanwezigheid van hypofyse uitval was de meest overheersende voorspeller voor verminderde kwaliteit van leven, alhoewel 93% van de patiënten wel enige vorm van hypofyse uitval had.

In de onderhavige studie vergeleken we groepen patiënten die in het verleden voor verschillende hypofyse adenomen zijn behandeld met controle personen en met elkaar. De studie toont aan, dat er een significant verminderde kwaliteit van leven is voor alle subschalen van de vier gezondheidsgerelateerde vragenlijsten bij alle patiënten vergeleken met 440 controle

personen met een vergelijkbare leeftijd en geslacht. Bovendien was de ervaren kwaliteit van leven gemeten met de totale kwaliteit van leven Z-score significant verschillend tussen de diverse patiënten groepen met verschillende hypofyse adenomen. Deze was het slechtste bij patiënten behandeld voor acromegalie vergeleken met patiënten behandeld voor niet-functionerend hypofyse macroadenoom of prolactinoom. De Z-scores over de onderdelen fysieke mogelijkheden en fysiek functioneren van de NHP en SF-36 vragenlijsten, werden negatief beïnvloed bij patiënten met acromegalie, vergeleken met patiënten met niet-functionerend hypofyse macroadenomen en prolactinomen. De patiënten met acromegalie hadden meer pijn vergeleken met patiënten met niet-functionerend hypofyse macroadenomen (SF-36). De Z-scores voor fysiek functioneren verschilde tevens tussen patiënten behandeld voor ziekte van Cushing en voor niet-functionerend hypofyse macroadenoom, met de grootste beperkingen bij patiënten met de ziekte van Cushing. Verder hadden patiënten, die behandeld waren voor de ziekte van Cushing, meer angst.

Het persisteren van fysieke en psychologische beperkingen beïnvloedt de kwaliteit van leven in alle patiënten met hypofyse adenoom, ondanks langdurige controle of biochemische curatie. Het vrouwelijke geslacht en uitval van hypofyse hormonen waren geassocieerd met slechtere kwaliteit van leven. Patiënten met acromegalie ervaren de grootste verminderde kwaliteit van leven, voornamelijk ten gevolge van beperkingen in fysieke prestaties en toegenomen pijn. De langdurige blootstelling aan verhoogd groeihormoon gehaltes in het verleden liggen zeer waarschijnlijk ten grondslag aan de irreversibele veranderingen in gewrichten.

Klinische implicaties. Patiënten met hypofyse adenomen hebben, ondanks langdurige biochemische controle c.q. curatie en adequate hormoonsubstitutie, beperkingen van de zelfgerapporteerde kwaliteit van leven. Het probleem is dat de uitingen van deze verminderde kwaliteit van leven niet eenvoudig zijn vast te stellen met klinimetrische methoden of endocrinologische bepalingen in plasma. Dit maakt het lastig om de uitingen van dit belangrijke onderwerp in de dagelijkse praktijk vast te stellen, terwijl juist door het miskennen van deze associatie de gevolgen van de ziekte op het leven van de patiënt over het hoofd gezien wordt. Dit kan natuurlijk nadelige gevolgen hebben voor de arts-patiënt relatie. De behandeling zou dan ook gericht moeten zijn op zowel biochemische controle c.q. curatie, als op verbetering van de sociale, psychologische en emotionele gevolgen voor de patiënt. Hierbij is het op dit moment het belangrijkste om zorgvuldige voorlichting aan patiënten te geven over deze lange termijn gevolgen van de behandeling van hypofyse adenomen, teneinde geen verkeerde verwachtingen bij de patiënten te wekken ten aanzien van de resultaten van de behandeling.

Maligne prolactinoom

Hypofyse adenomen zijn over het algemeen benigne aandoeningen zonder enige neiging om te metastaseren, ondanks het feit dat ze soms wel locaal invasief zijn. Echter, in zeldzame gevallen presenteren patiënten zich met een maligne transformatie van een hypofyse adenoom. In **hoofdstuk 6** wordt de presentatie, het klinische beloop en de histopathologische

karakteristieken van een patiënte met een zeldzame manifestatie van een maligne prolactinoom beschreven. De patiënte presenteerde zich in eerste instantie met dubbelzien, een afhangend rechter ooglid, en een verlamming van de n. abducens. Ondanks sequentiële behandeling met diverse soorten dopamine agonisten trad er een voortgaande stijging op van het prolactine gehalte, en was er invasieve groei van het macroadenoom te zien op de beeldvorming. Operatie middels craniotomie en aanvullende radiotherapie resulteerden in een daling van het prolactine gehalte. Echter na 14 maanden trad er wederom een stijging op van het prolactine gehalte. Een epidepride (dopamine D2 receptor) scintigrafie toonde intracraniele en extracraniële (spinale) pathologische stapeling, als uiting van metastasen. Deze spinale metastasen werden bevestigd middels histopathologisch onderzoek van het weefsel verkregen tijdens een laminectomie. Adjuvante behandeling met radiotherapie kon progressie van ziekte niet voorkomen met uitbreiding van de primaire hypofysaire tumor en de metastasen. Patiënte overleed 5 jaar na presentatie.

Een aantal kenmerkende eigenschappen van een maligne prolactinoom komen voort uit een gedetailleerde analyse van alle 47 casussen beschreven in de literatuur en deze huidige casus, waardoor een onderscheid met een "gewoon" prolactinoom mogelijk is. Ten eerste, het agressieve beloop met symptomen van compressie van hersenzenuwen, de aanwezigheid van een invasief adenoom op de MRI, en resistentie van adenoom en prolactine gehalte op dopamine agonisten bij presentatie. Ten tweede, de histopathologische bevindingen kunnen aanwijzingen bevatten voor maligne conversie. In retrospectie bleken de histopathologische bevindingen van de tumor verkregen bij de craniotomie en laminectomie een hoge proliferatie index te hebben met een Ki-67 labeling index van 10-15%. Histopathologische kenmerken die geassocieerd zijn met weefsel met een hogere proliferatie en agressief beloop zijn cellulaire atypie, nucleaire pleiomorfismen, meer dan twee mitosen per tien "high-powered fields", een Ki-67 index van 3% of meer, positieve p53 immunoreactiviteit, en perifere invasie (46;47). Deze parameters zijn weliswaar indicatief voor een eventueel agressief type adenoom, maar ze zijn niet conclusief voor de diagnose maligne prolactinoom. De diagnose maligne prolactinoom kan, helaas, alleen gesteld worden als de derde eigenschap optreedt, namelijk metastasering.

Een maligne prolactinoom heeft een slechte prognose met een gemiddelde overleving van slechts bijna twee jaar na het optreden van metastasen. Voorts blijkt dat aanvullende behandeling (chirurgie, radiotherapie, chemotherapie, octreotide, en/of dopamine agonisten) eigenlijk weinig invloed hebben op het natuurlijke agressieve beloop van de ziekte.

Voor wat betreft de ***klinische implicaties*** kan gesteld worden, dat het ontstaan van resistentie voor dopamine agonisten en/of groei van een prolactine producerend adenoom tijdens gebruik van dopaminergica, de clinicus alert zou moeten maken op de mogelijkheid van een maligne prolactinoom. Histopathologisch onderzoek van het tumor weefsel kan aanwijzingen hiervoor geven. Met name een hoge K-67 labeling index, p53 immunoreactiviteit en een hoge mitose index zijn geassocieerd met atypisch en agressief gedrag van de tumor, en kunnen de differentiaal diagnose maligne prolactinoom onderbouwen. Aanvullend onderzoek middels

beeldvorming van het gehele lichaam is aangewezen, alhoewel metastases zich meestal openbaren door gerichte beeldvorming op grond van locale klachten veroorzaakt door metastasen.

CONCLUDERENDE OPMERKINGEN

Dopamine agonisten waren de eerste effectieve medicamenteuze behandeling voor hypofyse adenomen. De algemene effectiviteit van deze behandeling was geassocieerd met het algemene denkbeeld van de behandelend arts dat de behandeling van prolactinomen louter bestond uit het voorschrijven van dopamine agonisten. Deze patiënten worden tegenwoordig dan ook door allerlei specialisten behandeld, zoals internisten, endocrinologen, kinderartsen en gynaecologen. Echter, de studies beschreven in dit proefschrift geven aan dat de behandeling van deze ziekte in alle opzichten verre van simpel is.

Zelfs patiënten met microprolactinomen en een adequate reactie op dopamine agonisten zijn vaak ontevreden over de behandeling, doordat ze een aanzienlijke verminderde kwaliteit van leven hebben. Deze ontevredenheid over de behandeling beïnvloedt dan ook vaak de arts-patiënt relatie negatief.

Langdurige controle van macroprolactinomen is ook geen rechttoe rechtaan behandeling, indien er sprake is van resistentie of intolerantie voor dopamine agonisten. In deze situaties kan het voorschrijven van een andere dopamine agonist noodzakelijk zijn. Indien dit niet afdoende is, kan chirurgische behandeling als tweedelijns behandeling worden toegepast. In enkele situaties zal een additionele behandeling met postoperatieve radiotherapie nodig zijn. Echter, deze tweede- en derdelijns behandelingen gaan gepaard met een veel hogere incidentie van hypofyse uitval. Daardoor zullen deze behandelstrategieën de kwaliteit van leven verder negatief beïnvloeden.

Langdurige behandeling van prolactinomen is geassocieerd met een verhoogde kans op milde tricuspidalis regurgitatie en calcificaties van de aortaklep, hoewel dit niet gepaard gaat met klinisch relevante klepafwijkingen. Alhoewel de klinische relevantie van deze observatie momenteel nog onduidelijk is, moet er niet te licht over gedacht worden. Gedurende langdurige follow-up is slechts 22% van de patiënten met macroprolactinoom genezen, dat wil zeggen zonder het gebruik van dopamine agonisten. Bij de overige patiënten is voortgezette behandeling met dopamine agonisten noodzakelijk. Het kan bij aanvullende studies mogelijk blijken dat dit uiteindelijk schadelijke effecten heeft op hartklep functies.

Ten slotte, in extreem zeldzame situaties kan het klinisch beloop van een prolactinoom zich gecompliceerd en agressief gedragen, welke de clinicus alert zouden moeten maken op het mogelijk bestaan van een maligne prolactinoom.

De studies gepresenteerd in dit proefschrift geven aan dat patiënten met een prolactinoom behoefte hebben aan langdurige toegewijde zorg.

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NAWOORD

Bestemming bereikt!! Het schrijven van een proefschrift is als een luchtballonvaart: je stippelt wel een route uit, maar gaande weg is men overgeleverd aan de richting en de kracht van de wind. Het vereist een goed kompas en een zekere ballast, en het is een onderneming waar ongemerkt vele mensen aan bijdragen.

Allereerst de patiënten met prolactinoom onder behandeling op de polikliniek Endocrinologie van Leids Universitair Medisch Centrum, zonder wie het niet mogelijk zou zijn geweest de klinische studies te verrichten. Mijn dank is groot! Ik hoop een bijdrage te hebben geleverd aan het vergroten van inzicht in de ziekte prolactinoom, het beloop en mogelijke bijwerkingen van medicatie.

Al tijdens mijn studie geneeskunde aan de VU in Amsterdam werd ik door Prof. Netelenbos en Prof. Lips geïnspireerd voor het vakgebied endocrinologie. Nadat ik enkele jaren in opleiding was tot internist, kreeg ik de mogelijkheid het aandachtsgebied te volgen binnen de afdeling Endocrinologie van het Leids Universitair Medisch Centrum, gecombineerd met een promotieonderzoek. De sfeer van de afdeling was al snel duidelijk: stimulerend en altijd gelegenheid voor overleg!

Het enthousiasme waarmee zowel de begeleiding voor de opleiding, als het onderzoek gepaard ging, heeft ervoor gezorgd dat deze ballonvaart koersgericht en vlot verliep. Mijn horizon werd verbreed door de nodige discussies, wat tevens resulteerde in waardevolle adviezen met betrekking tot het opzetten van het onderzoek en het schrijven van de manuscripten. Boven alles maakten humor en gemeende interesse in het leven van de promovendus buiten de muren van het ziekenhuis, deze vaart tot een zeer plezierige samenwerking!

Marjan Wassenberg en Moniek Kars, ik ben zeer verheugd en vereerd dat jullie mijn paranimfen willen zijn. Naast alle onderzoeksperikelen, hebben we de afgelopen jaren ook heel wat persoonlijke momenten gedeeld, soms met een traan, maar meestal met een lach!

Binnen de afdeling Endocrinologie zijn er talloze mensen die ik wil bedanken: de secretaresses Caroline, Marianne, en Marjolein; de altijd opgewekte afdelingssecretaresse Ingrid, de geduldige dames van de polikliniek Marja, Chantal, Anneke, Angelique, Anneke Veldhuyzen, en Wanda.

Agatha: "even bijkletsen" tussen de poli's door resulteerde vaak in urenlange gesprekken waarin onderzoeksgerelateerde issues bliksem snel werden afgewisseld met privé zaken. Het klikte meteen! Gelukkig heeft Cambridge, en ik hoop ook St. Louis, daar geen verandering ingebracht.

Eveline en Marieke, jullie zou ik samen met Agatha, een soort superparanimfen kunnen noemen, zelfde interesses, onvermoeibaar om al mijn gezeur aan te horen, en altijd behulpzaam!

Olaf, elke p-waarde heeft ook een waarde, alleen wist jij die natuurlijk altijd beter in te schatten dan ik. Ik begreep er soms geen p-waarde van, maar goed daar had ik jou dan natuurlijk weer voor. Dank voor je statistisch significante bijdragen,en al je chocolade. Overigens is gebleken dat je bijnieren *kunt* ontwikkelen.

De sfeer was altijd goed met mijn kamergenoten op de afdeling Endocrinologie, waarvoor dank: Peter, Thomas, wij weten dat muizen- en kliniekmensen best gecombineerd kunnen worden, niet alleen op de werkvloer, maar ook zeker bij de nodige borrels. Peter, jij voorzag op "mijn" kamer ons van de nodige calorische snacks, koekjes, en wederom mijn verslaving chocolade.

Patiëntenzorg en diensten werden afgewisseld met onderzoek. Gelukkig deed ik dit niet alleen, maar kon ik de werklast delen met mijn "medefellows": Bas, dank voor de heerlijke samenwerking tijdens ons aandachtsgebied, Nienke en Behiye.

Eigenlijk is het allemaal begonnen in Amersfoort, in het Meander Medisch Centrum waar Carlo Gaillard als mijn mentor mij door de eerste jaren van de opleiding heen leidde, waarvoor grote dank! Vervolgens Mark Kramer, die mij aanspoorde om toch vooral in Leiden bij Prof. Romijn te gaan solliciteren.

En waar hechte vriendschappen zijn ontstaan: Anouk, Dylan, Marjan, Leontine, Wouter, George, Stijn en Lidwine, het was met recht een onvergetelijke tijd. Ik waardoor het enorm dat ik de afgelopen jaren, en ik hoop nog vele jaren in de toekomst, van jullie vriendschap mag genieten.

Mijn Ouderwaterse Meiden, heel bijzonder, en zeer gekoesterd dat we elkaar en onze vriendschap de afgelopen 20-25 jaar trouw zijn gebleven. Een half woord, met soms een enkele blik, is vaak genoeg om elkaar te begrijpen, en daar ben ik jullie enorm dankbaar voor: Tamara, Marlou, Susanne, Rianne, Amber, Marije, Jennifer, Renate, Cindy en Judith.

Niemand kan zonder familie: Oma, Pa, Ma, Mieke, Maarten en Moniek, en natuurlijk ook Florian en Melle.

Pa, Ma, Mieke, Maarten en Moniek: dieptepunten en hoogtepunten hebben we samen beleefd, en jullie steun was in welke situatie dan ook onvoorwaardelijk. Ik bewonder jullie allemaal voor wat jullie ieder voor zich in je privé en in je "werk" leven hebben bereikt. Een echte Kars zet door, en dat hebben we allemaal wel laten zien.

Lieve Oma, bij jou is het eigenlijk allemaal begonnen. Jij, met die eigenschappen waar ik je enorm om bewonder: trots, eigenwijs en een enorme doorzetter, vertelde je me al van jongs

af aan al je avonturen in het ziekenhuis. Ik herkende in die verhalen tijdens mijn studie, coschappen, en opleiding tot internist de gedrevenheid die jij vroeger in je had, het gevoel om voor andere te zorgen en naar perfectie te streven. De afgelopen jaren vond je zeker dat ik te hard werkte, en had je liever gehad dat ik wat vaker langs was gekomen, maar dat maak ik allemaal goed met je. Ik hoop dat we samen nog vele mooie momenten mogen beleven.

Florian en Melle, jullie laten de dag stralen als geen ander!

CURRICULUM VITAE

Marleen Kars werd geboren op 9 december 1975 te Oudewater. Na in 1994 het VWO diploma behaald te hebben op het Sint Antonius College te Gouda, studeerde ze Geneeskunde aan de Vrije Universiteit te Amsterdam. In 1998 werd het doctoraal examen afgelegd, en na het volgen van een aantal klinische stages bij de vakgroepen Endocrinologie en Kinderendocrinologie in het VU Medisch Centrum, werd in 2000 het artsexamen behaald. Aansluitend was zij bijna 2 jaar werkzaam als arts-assistent interne geneeskunde in het Meander Medisch Centrum te Amersfoort. De opleiding tot internist werd in 2002 begonnen in het Meander Medisch Centrum te Amersfoort (opleider Dr. A. van de Wiel), welke in januari 2005 werd voortgezet in het Leids Universitair Medisch Centrum te Leiden (opleider Prof.dr. J.A. Romijn), alwaar tevens een start werd gemaakt met het onderzoek dat geleid heeft tot dit proefschrift (promotor Prof.dr. J.A. Romijn). In oktober 2005 startte zij met het aandachtsgebied Endocrinologie in het Leids Universitair Medisch Centrum te Leiden (opleider Prof.dr. J.W.A. Smit), welke zij in oktober 2007 afrondde, tegelijkertijd met de opleiding tot internist. Vanaf maart 2008 zal zij werkzaam zijn op de afdeling Internal Medicine, Division of Geriatrics & Nutritional Science, Washington University School of Medicine te Saint Louis (USA, MO).

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