Pituitary adenomas, some diagnostic and therapeutical aspects

• A.J. van der Lely, W.W. de Herder and S.W.J. Lamberts

Introduction

Pituitary adenomas are frequently occurring neoplasms. In unselected pituitaries of adults obtained post-mortem a prevalence from 6 up to 23% is recorded [1 2]. Using immunocytochemical techniques, the prevalence of different types of pituitary adenomas could be estimated in large series of surgically removed pituitary tumours (see Table 1) [3 4]. While most pituitary adenomas are histologically benign, slow-growing tumours, some adenomas show a more rapid growth, with extension into the surrounding tissues, eventually causing damage to the optic nerve(s) and/or other cranial nerves [5]. In this manuscript some aspects of the treatment and problems which can occur during treatment of each of the pituitary adenomas, as mentioned in Table 1, will be described.

Prolactinomas

Diagnosis

As mentioned in Table 1, prolactinomas account for approximately 30% of pituitary adenomas. There are many reasons for an elevated serum prolactin level, such as pregnancy, renal failure, primary hypothyroidism, or the use of medication known to induce hyperprolactinaemia (see Table 2). As prolactin is the only hormone of which the production is under constant suppression by dopamine, a sellar abnormality in a patient with hyperprolactinaemia may be due not only to a prolactinoma, but also to pituitary tumours or hypothalamic disorders, which decrease dopamine levels (*e.g.* by compression of the pituitary stalk). As serum prolactin levels do correlate well with the size of the prolactinoma, a mild degree of hyperprolactinaemia in association with a macroadenoma, particularly with extrasellar extension, is usually not consistent with a prolactinoma, but with *e.g.* a non-functioning pituitary adenoma [6].

Treatment

The natural history of untreated hyperprolactinaemia is not clear [7]. Therefore, in patients with untreated microadenomas, clinical symptoms, serum prolactin levels, and the appearance of the pituitary gland must be carefully monitored. In many patients with prolactinomas abnormalities in the secretion of gonadotropin-releasing hormone (GHRH) and gonadotropins lead to a relative or absolute oestrogen deficiency [8]. This is associated with osteoporosis, so despite the relative stability in tumour size, preventive therapy of hyperprolactinaemia may be necessary. Although only high oestrogen dosages can cause a mild hyperprolactinaemia, the use of oestrogens (*e.g.* as an oral anticonceptive drug) is not advisable. Therapy may also be necessary because of reproductive dysfunction, infertility, galactorrhoea, as well as sexual dysfunction. Treatment of adenomas primarily consists of dopaminergic drugs. Neurosurgery is not the treatment of first choice because of the very high percentage of recurrence [9]. Radiation therapy for

Van der Lely AJ, De Herder WW, Lamberts SWJ. Pituitary adenomas, some diagnostic and therapeutical aspects. Pharm World Sci 1994;16(5):201-7.

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Keywords
Adenoma
Adverse effects
Diagnosis
Dopaminergic agents
Hormone antagonists
Ketoconazole
Octreotide
Pituitary diseases

Abstract
The treatment of almost all types of pituitary adenomas has changed considerably in recent years. New types of drugs as well as improved application forms of older drug therapies are now becoming more and more available for everyday treatment of patients with these relatively rare diseases. For the most frequently occurring pituitary adenomas the drugs of first choice are described, as well as other available treatments, their indications and efficacies. Also the main side-effects are described.

Accepted July 1994.

Table 1 *Estimated prevalence of different types of pituitary adenomas derived from large series of surgically removed pituitary tumours*

Type of pituitary tumour	*Prevalence (%)*
Prolactinomas	25-30
Tumours secreting growth hormone	15-35
Tumours secreting follicle-stimulating hormone/luteinizing hormone	4
Tumours secreting corticotropin (ACTH)	15
Tumours secreting thyroid-stimulating hormone	< 1
Non-functioning tumours (no or few hormone-positive cells could be detected)	20-30

prolactinomas is also unattractive, because of the associated hypopituitarism and the proven efficacy of drug therapy [10 11].

Bromocriptine

Bromocriptine directly stimulates dopamine receptors (mainly D_2 receptors) [12]. Bromocriptine is capable of improving visual disturbances and reducing tumour size objectively in patients with large prolactinomas within several days or weeks [13]. It reduces tumour size by 50% or more in about 50% of the patients with a macroprolactinoma and decreases prolactin levels to normal in about 70% of the patients [14]. Discontinuation of the therapy may be associated with a rapid expansion of tumour size and an increase in prolactin levels, so most patients require dopaminergic therapy indefinitely [15]. However, bromocriptine can be discontinued every two years on a trial basis to determine the need for continued therapy, as hyperprolactinaemia can resolve spontaneously.

Side-effects, which are roughly the same for all of the dopaminergic drugs, are nausea, orthostatic hypotension, headaches, fatigue, nasal congestion, abdominal cramps and constipation. Rare side-effects are pulmonary fibrosis, vasospasms and psychosis in patients with underlying psychiatric disorders [16]. The occurrence of side-effects, as well as the need for two or three daily doses of bromocriptine, remain important problems in the treatment of prolactinoma patients. Therefore, other dopaminergic drugs have been developed recently, including metergoline, lisuride, pergolide, mesulergine, terguride, dihydroergocristine, dihydroergocriptine, cabergoline and quinagolide. Metergoline, dihydroergocristine and terguride were less effective than bromocriptine [17-19], while lisuride and mesulergine were more poorly tolerated than bromocriptine [20 21]. Cabergoline, pergolide and quinagolide will be discussed in more detail.

Table 2 *Drugs that can cause mild hyperprolactinaemia*

Antidepressant drugs (*e.g.* amitriptyline, imipramine)
Antihypertensive drugs (*e.g.* methyldopa)
Opiates
Oestrogens (in high dosages)
Neuroleptics (*e.g.* perphenazine, haloperidol)
Dopamine receptor-blocking agents (*e.g.* domperidone, metoclopramide)
Histamine H_2 receptor antagonists

Cabergoline

A single oral dose of 0.3-0.6 mg cabergoline significantly lowers prolactin levels in hyperprolactinaemia for 7-14 days [22]. Given in a dose of 0.4-3.0 mg at weekly intervals for 8-9 weeks cabergoline induces normalisation of prolactin levels in about two thirds of hyperprolactinaemic women [23]. It has been shown that most patients are able to tolerate effective doses of cabergoline without important side-effects [24 25]. These results indicate that cabergoline is a well-tolerated new dopaminergic drug with long-lasting activity which represents a potential advantage in the chronic treatment of hyperprolactinaemic states.

Pergolide

The dopaminergic drug pergolide produced long-lasting reductions in prolactin levels after single doses of 50 μg [26]. After 24 hours, the values remained suppressed at a mean of 29% of the baseline value. Liver enzyme disturbances were recorded infrequently. Although pergolide is a potent inhibitor of prolactin secretion [27], the drug has never found an important place in the treatment of hyperprolactinaemic states. In a double-blind study involving a total of 157 hyperprolactinaemic patients the efficacy and tolerability of bromocriptine and pergolide were found to be the same, while the incidence and type of side-effects to both dopamine agonists were similar [28].

Quinagolide

Quinagolide (an octahydrobenzo[g]quinoline) is a non-ergot alkaloid dopaminergic drug, which recently became available for the therapy of hyperprolactinaemic states [29]. It is a potent D_2 receptor agonist, with only a weak D_1 receptor activity. On a weight basis this drug is far more potent than bromocriptine in suppressing both normal and pathological prolactin secretion [30 31]. These promising results were confirmed in several studies, all showing the potent inhibitory effect of quinagolide on prolactin secretion, as well as on tumour size, both in microprolactinoma and in macroprolactinoma patients. Only relatively few patients complained of side-effects so severe that drug therapy had to be discontinued [32-34].

Conclusion

The treatment of prolactinomas has improved dramatically in the last 20 years. Transsphenoidal hypophysectomy as primary treatment is hardly ever indicated nowadays. Dopaminergic drugs are effective enough to control increased prolactin production and tumour growth in the vast majority of patients. Considerable tumour shrinkage occurs in most patients. An important problem remains that bromocriptine has considerable side-effects, which result in a decrease in compliance in part of the patients. The development of newer, more specific dopamine D_2 receptor agonists, *e.g.* quinagolide, were shown to be an improvement in the therapy of macroprolactinomas in particular, with regard to both the lower incidence of side-effects and compliance, because this drug can be taken once daily.

Cushing's disease

Diagnosis

When Cushing's syndrome is suspected, two excellent screening tests are available: the overnight dexamethasone test [35] and the measurement of 24-hour urinary excretion of cortisol [36]. After hypercortisolism has been confirmed in a patient with clinical Cushing's syndrome, the site of hormone overproduction must be determined. Once causes of Cushing's syndrome like medication (corticosteroid therapy), alcohol abuse *etc.* have been shown unlikely, one must determine whether Cushing's syndrome is caused by Cushing's disease (pituitary overproduction of corticotropin), ectopic production of corticotropin (or corticotropin-releasing hormone) or overproduction of cortisol by an adrenal tumour (adenoma or carcinoma).

To determine whether Cushing's syndrome has a pituitary or non-pituitary cause can be very difficult. A continuous dexamethasone infusion (1 mg/h) for 7 h seems to be a superior diagnostic tool for this differential diagnostic problem [37]. The corticotropin-releasing hormone stimulation test is also a reliable test with high sensitivity and specificity [38]. Magnetic resonance imaging seems to be a better way of localizing pituitary corticotropin-secreting microadenomas than computer-tomographic scanning [39 40]. A major advance in the diagnosis of Cushing's disease has been sampling of corticotropin in both inferior petrosal sinuses and measuring the central-to-peripheral corticotropin ratio [41 42].

Bilateral catheterization of the inferior petrosal sinus before surgery is recommended in all patients for whom dynamic testing is consistent with pituitary tumour but imaging studies are inconclusive.

Treatment

The therapy of choice for patients with Cushing's disease is selective transsphenoidal adenomectomy. The reported rates of surgical cure are as high as 90% in patients with microadenomas. If sellar exploration does not reveal a tumour, hemihypophysectomy can be performed with the use of the lateralization data obtained from preoperative bilateral measurement of corticotropin in the inferior petrosal sinuses. Primary conventional radiotherapy leads to biochemical and clinical improvement in only 15 to 25% of adult patients [43] while neurological complications occur relatively frequently.

Drug therapy of patients with Cushing's disease may be used to control severe hypercortisolism before curative surgery, as an adjunctive treatment in patients who have received radiotherapy, or to treat patients who are not surgical candidates. Agents that inhibit the production of cortisol are also useful in the treatment of patients with ectopic corticotropin syndrome. A number of pharmacological agents block the adrenal system.

Metyrapone

Metyrapone is an 11β-hydroxylase inhibitor, which decreases cortisol secretion, while the production of 11-deoxycortisol and dehydroepiandrosterone is increased [44]. It has been used in the treatment of Cushing's disease. In doses up to 2 g daily, biochemical and clinical remission can be achieved [45]. Nausea, vomiting and dizziness can occur. The drug can also cause hirsutism due to the overproduction of adrenal androgens, as well as hypertension, hypokalaemic alkalosis and oedema, due to the accumulation of 11-deoxycortisol.

Aminoglutethimide

Although originally developed as an anticonvulsant drug, aminoglutethimide is now also used as a drug against hypercortisolism. It inhibits primarily the cholesterol side-chain cleavage enzyme which is involved in the synthesis of corticosteroids as well as the aromatase enzyme which converts androgens to oestrogens. It causes gastrointestinal side-effects, somnolence and a transient rash in therapeutical doses of 1-2 g daily. Steroid withdrawal symptoms are inevitable and replacement therapy by corticosteroids is required [46]. However, in the long term, the use of this agent is limited by its lack of therapeutic efficacy and by side-effects, including gastrointestinal symptoms and (often severe) somnolence.

Ketoconazole

Ketoconazole, an antimycotic agent, is an imidazole derivative which inhibits mitochondrial cytochrome P-450 enzymes. The major activity appears to be the inhibition of 17-20 desmolase. A moderate blockade of 17-hydroxylase may be present, while there is a marked inhibition of 21- and/or 11-hydroxylase. It thus inhibits the conversion of androgens to oestrogens, of progesterone to androstenedione and testosterone, and of 11-deoxycorticosterone to corticosterone [47]. Started in doses of 800-1,200 mg daily and with maintenance doses of 600-800 mg daily, ketoconazole is relatively well tolerated, although liver enzyme disturbances can be a problem. It has been proven to be effective in the treatment of hypercortisolism in most types of Cushing's syndrome [48-51]. One potential benefit of ketoconazole is that while the cortisol levels decrease, there is not necessarily a proportionate increase in corticotropin levels. It is felt that ketoconazole may have a pituitary effect on decreasing corticotropin secretion [52]. Ketoconazole should be considered the initial drug therapy of choice in the majority of patients with Cushing's syndrome who require adjunctive treatment. However, the effects of long-term use have not been established.

Mifepristone

The properties of mifepristone (RU 38486, RU 486), a steroid with powerful blocking activity at the progesterone and the glucocorticoid receptor, have been studied both *in vitro* and *in vivo* [53]. In normal humans, mifepristone blocks glucocorticoid negative feedback at the hypothalamic–pituitary level, inducing a compensatory increase in plasma corticotropin and cortisol levels [54]. After one single-dose oral gift of 400 mg, mifepristone induces a response that lasts at least 34 h. When ketoconazole is unable to lower cortisol production and if the clinical condition requires a rapid, more or less acute total blockade of cortisol receptors (*i.e.* acute psychosis), the use of mifepristone should be considered [55]. Unfortunately, the drug cannot be titrated very well because there are no objective biological parameters to measure its effects. The blocking effects on the cortisol receptor in man can be antagonized by very high doses of dexamethasone [56].

Conclusion

The treatment of Cushing's syndrome depends entirely on its cause. The diagnosis of Cushing's syndrome due to ectopic corticotropin or corticotropin-releasing hormone production seems to be improved by the introduction of new procedures, like petrosal sinus catheterization and the use of magnetic resonance imaging. Also, several new drugs have become available. Both drugs blocking adrenal cortisol production (*e.g.* ketoconazole) and cortisol receptor blocking agents like mifepristone seem to have a place in the treatment of Cushing's syndrome. These drugs are better capable of controlling the clinical effects of hypercortisolism in Cushing's syndrome than the older ones. They still have considerable side-effects and, in the case of mifepristone treatment, monitoring the degree of cortisol receptor blockade is difficult, if not impossible.

Non-functioning tumours

Diagnosis

The majority of so-called non-functioning pituitary adenomas are slowly growing macroadenomas with extrasellar extension. As such tumours do not have a characteristic clinical syndrome of excessive hormone production, they can grow to a considerable size before they are detected. Symptoms like headache, insidious visual loss and hypopituitarism are the most frequent occurring symptoms. These tumours present themselves at a relatively high age (50-80 years) [57]. When they produce gonadotropins, they are called gonadotropinomas. The pituitary glycoprotein hormones are composed of a common α subunit as well as β subunits specific to each hormone. The elevation of serum α or β subunit concentrations therefore seems to be an independent tumour marker and independent of alterations in the levels of other pituitary hormones. In some cases a paradoxical rise in one or several of these hormones to thyrotropin-releasing hormone can be helpful in establishing the diagnosis [58].

Treatment

As most of the clinically non-functioning pituitary adenomas present themselves with visual field defects, neurosurgical decompression is often necessary. In principle the transsphenoidal approach is the primary therapy, although recent publications of experienced groups do report a considerable perioperative risk [59 60].

Pharmacotherapeutic possibilities with these tumours are somatostatin analogues, like octreotide, and dopaminergic drugs [61 62]. Possibly in the future gonadotropin-releasing hormone antagonists will also be of potential therapeutic use [63].

Octreotide

Experience with octreotide is limited and consist of only some case reports. In most cases no reduction in tumour size was seen, but, remarkably, a fast improvement in visual capabilities was described in some patients. Whether this is the result of just a very small reduction in tumour size or a direct effect of octreotide on the retina or optic nerve is presently unknown.

Quinagolide

In a recent report in a small group of 5 patients with clinically non-functioning pituitary adenomas the use of the dopaminergic drug quinagoline was investigated. Both an improvement in visual disturbances and a decrease in tumour size and a significant decrease in gonadotropin and/or subunit levels was observed [64]. Larger studies are necessary, though, to confirm these results.

Conclusion

The treatment of non-functioning tumours of the pituitary gland is primarily a surgical one, largely because of the size of these tumours, often leading to panhypopituitarism and visual disturbances. If these complications are not present, one can be more conservative. Hopefully in the future more results will become available proving beneficial results of treatment with dopaminergic drugs and/or somatostatin analogues.

Acromegaly

Diagnosis

Although human somatic growth is regulated primarily by growth hormone, most of its growth-promoting effects are mediated by insulin-like growth factor I (IGF-I), which is largely synthesized in the liver, but is also produced in the kidney, muscle, pituitary gland, chondrocytes and the gastrointestinal tract [65]. As a negative feedback mechanism, IGF-I suppresses growth hormone-mRNA synthesis in the pituitary gland [66]. Although most of the growth hormone's growth-promoting actions are mediated by IGF-I, animal models suggest that the hormone and IGF-I act independently and synergistically in skeletal and organ growth [67].

Because of the apparent manifestation of the disease, acromegaly is usually diagnosed clinically. In most studies a positive correlation between tumour size and basal growth hormone levels has been found [68 69]. Up to levels of about 50-80 µg/l,

growth-hormone concentrations correlate well with serum IGF-I levels, suggesting that growth-hormone levels of about 60 μg/l stimulate IGF-I production maximally [70 71]. Several authors have reported a correlation between age and tumour volume, while others could not find such a relationship [72].

The two most sensitive tests for biochemical confirmation of the hypersecretion of growth hormone are measurements of plasma IGF-I and an oral glucose tolerance test, which is more time-consuming but still is the golden standard. Random determinations of growth-hormone levels are rarely useful in the diagnosis of acromegaly. For screening purposes, IGF-I levels are specific in the diagnosis of acromegaly, as they correlate well with mean 24-hour plasma growth-hormone concentrations.

Treatment

As acromegaly is associated with an increase in the expected mortality rate [73], it has to be treated either by surgery, drug therapy or radiotherapy (or any combination of these). Considering the fact that 50% of the patients with growth-hormone levels < 5 μg/l after surgery, do still have elevated IGF-I levels [74], a real cure of acromegaly by surgery might be rare. So other means of therapy or combinations of therapy are often necessary. When increased growth-hormone production still persists after surgery, or when there are contra-indications for surgery, external conventional radiotherapy can be used as treatment. This method is capable of reducing growth-hormone levels in a majority of the patients to < 5 μg/l, although normal growth-hormone levels are only reached after several years [75]. Acquired hypopituitarism as a (late) complication of radiation therapy occurs in more than 50% of the patients [76].

Bromocriptine

As relatively large doses of bromocriptine are necessary to induce clinically beneficial effects [77] this drug is not so often used as a primary therapy for acromegaly, but more often as an adjuvant therapy [78]. In less than 20% of the patients, bromocriptine is capable of reducing growth-hormone levels to less than 5 μg/l, while only in 8% of the patients normalization of IGF-I levels is achieved.

Octreotide was found to be more effective in lowering growth-hormone levels than bromocriptine [79]. In a recent study by Chiodini *et al.* quinagolide was as potent in reducing growth-hormone levels as bromocriptine. No patients insensitive to bromocriptine were sensitive to quinagolide [80].

Octreotide

Since the introduction of octreotide, therapy of acromegaly has become much more successful [81]. Octreotide (50 μg as a single dose, subcutaneously), suppresses growth-hormone secretion within 1 h. Maximal suppression of growth-hormone levels is reached after 3 h. The response may be sustained up to 12 h [82]. The drug reduces tumour volume in 50% of the patients [83]. It reduces growth-hormone secretion in 90% of the acromegalic patients, normalizes IGF-I levels in 60% and, because the course of serum growth-hormone levels after a single dose of octreotide correlates well with the serum growth-hormone levels reached during long-term treatment with octreotide, this substance has become the drug of first choice in the medical treatment of acromegaly [84]. It is usually well tolerated, although it inhibits gallbladder contractility, causing the development of gallstones [85]. It decreases headaches in most patients and long-term therapy with octreotide reduced serum IGF-I levels in several groups of acromegalics by 37 to 81%.

Good selection of patients by age, sex and tumour size is necessary. Not all patients need a transsphenoidal operation, which has its own morbidity and appears to be seldom radical in large invasive adenomas. Especially in older (male) acromegalic patients one can probably primarily choose for octreotide therapy and omit transsphenoidal surgery. Also, one can predict the ultimate efficacy of octreotide therapy in controlling hormonal hypersecretion by monitoring the degree of decrease of growth-hormone secretion after a single dose of octreotide.

Other somatostatin analogues, such as the long-acting BIM 23014, are tested for their usefulness in acromegaly now and some reports describe a potentially beneficial role [86].

Conclusion

The treatment of acromegaly has considerably improved after the introduction of octreotide. Control of hormonal hypersecretion can also be achieved in part of the patients by octreotide therapy. If tumour size is a problem on its own, octreotide is not the treatment of choice, because the extent of tumour shrinkage is in most instances disappointing. In this case surgery (often in combination with radiotherapy) is mandatory. After surgery octreotide therapy should be considered in order to control clinical symptomatology related to residual acromegaly.

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