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REVIEW

Update in prolactinomas

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ABSTRACT

Prolactinomas are a frequent cause of gonadal dysfunction and infertility, especially in women. Dopamine agonists are first-line therapy and their efficacy in the treatment of prolactinomas is well established. Current challenges related to the management of prolactinomas remain in the recurrence of the disease after withdrawal of dopamine agonists, the potential of increased risk of cardiac valvulopathy, which is observed in patients treated with high-dose cabergoline for Parkinson's disease, the effects of pregnancy, and impaired quality of life associated with pituitary adenomas in general, and prolactinomas in particular. Although most prolactinomas are biochemically well controlled by pharmaceutical treatment, long-term follow-up is required.

KEYWORDS

Prolactinomas, dopamine agonist, valvulopathy

PROLACTIN AND CAUSES OF HYPERPROLACTINAEMIA

Prolactinomas are adenomas derived from lactotroph cells in the pituitary gland, and are characterised by hypersecretion of prolactin. Unlike the other anterior pituitary hormones, the hypothalamic control of prolactin production and release is mediated by tonic inhibition by dopamine.[1] Normal prolactin concentrations in women and men are, depending of the assay used, below 25 µg/l and 20 µg/l, respectively.[2] Prolactin is not exclusively produced by the lactotroph cells in the pituitary gland. The largest portion of prolactin is produced outside the pituitary gland (extrapituitary prolactin), including hair follicles, adipose tissue and immune cells. Prolactin may act as a hormone, by the classic endocrine pathway, and as a growth factor, neurotransmitter, or immunoregulator, by autocrine or paracrine mechanisms. The primary action of prolactin is stimulation of lactation after delivery.

Hyperprolactinaemia can be caused by physiological processes, pharmacological effects, and pathological effects. Physiological causes of hyperprolactinaemia include pregnancy, physical or psychological stress, and breast stimulation. Drugs that stimulate dopamine receptors on lactotroph cells (e.g. metoclopramide, phenothiazides) or those that inhibit dopamine release from the hypothalamus (e.g. monoamine oxidase inhibitors, tricyclic antidepressants, serotonin re-uptake inhibitors), induce hyperprolactinaemia. In general, drug-induced hyperprolactinaemia is relatively mild with plasma prolactin concentrations up to 100 µg/l.[3] Hyperprolactinaemia can be caused by prolactinomas. Compression of the pituitary stalk due to suprasellar extension of craniopharyngioma, meningeoma, nonfunctioning macroadenomas, or severe head trauma can disrupt dopamine transport to the pituitary, and result in hyperprolactinaemia. Furthermore, primary hypothyroidism can cause hyperprolactinaemia due to increased synthesis of thyrotropin-releasing hormone, stimulating prolactin secretion. Other conditions associated with increased circulating prolactin concentrations are chronic renal failure and liver cirrhosis.

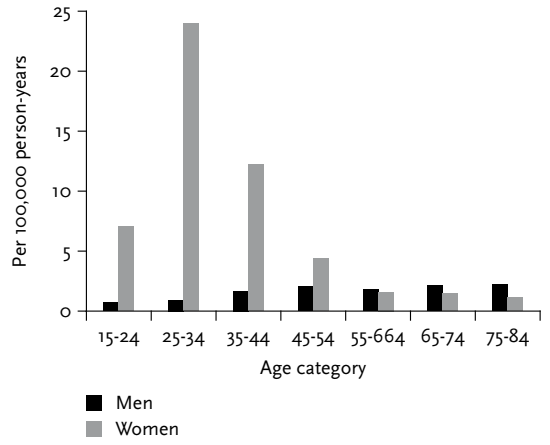
High concentrations of prolactin can also be explained by macroprolactinaemia. This refers to the presence of elevated concentrations of prolactin of high molecular mass, mostly due to complexes of monomeric prolactin with immunoglobulins (prolactin-autoantibody complexes). These larger molecules have no bioactivity and prolonged clearance

rate similar to that of immunoglobulins. Depending on the immunoassay used, macroprolactinaemia accounts for up to 25% of biochemically documented hyperprolactinaemia.[4] This indicates that macroprolactinaemia represents a common diagnostic pitfall. Consequently, in the initial diagnostic phase of hyperprolactinaemia, 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 exclude the presence of macroprolactinaemia. In case of macroprolactinaemia, the prolactin concentrations will decrease to normal after PEG precipitation.

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 to 100 per million inhabitants.[5] Recently, higher prevalence rates of 44 to 62 per 100,000 inhabitants have been reported.[6,7] We recently estimated the gender-specific prevalence in a large population-based Dutch cohort.[8] The prevalence of dopamine agonist-treated prolactinomas in female patients was almost five times higher (94 per 100,000) compared with male patients (20 per 100,000). Estimated incidence rate of dopamine agonist-treated prolactinoma was 8.7 per 100,000 person-years for women and 1.4 per 100,000 for men. The highest incidence rate was found in women between 25 and 34 years of age: 23.9 per 100,000 person-years (*figure 1*). A possible explanation for this higher prevalence of prolactinomas in premenopausal women is the higher likelihood of diagnosing hyperprolactinaemia in women of reproductive age because it presents with symptoms such as oligo/amenorrhoea and infertility. In contrast, in men symptoms are more subtle and/or even nonexistent, except when the tumour size causes signs of pituitary gland enlargement, such as headache and visual field defects. Whereas women present with microprolactinomas in the majority of cases, most men present with macroprolactinomas. This difference is probably caused by the subtle clinical symptoms in men in the early course of the disease.

Figure 1. *Incidence of patients with dopamine agonist (DA)-treated hyperprolactinaemia per 10 year age category for men and women from 1996 until 2006*



***Adapted from Kars M. et al. Estimated Age- and Sex-Specific Incidence and Prevalence of Dopamine Agonist-Treated Hyperprolactinemia. J Clin Endocrinol Metabol. 2009 Aug; 94(8):2729-34. Copyright 2009, The Endocrine Society.**

PATHOGENESIS OF PROLACTINOMAS

Hypotheses concerning the pathogenesis of prolactinomas include decreased stimulation by dopamine (dopaminergic receptor or postreceptor dysregulation) and clonal somatic mutations.[1] There are several arguments against the first hypothesis. First, decreased dopamine delivery to the pituitary due to long-term use of neuroleptic drugs or pituitary stalk compression does not induce prolactinomas. Second, most adenomas are only confined to a certain portion of the pituitary gland rather than characterised by widespread hyperplasia of prolactin producing pituitary cells. Third, after initial cure of the adenoma, e.g. by surgery, there is a low recurrence rate of adenoma. The local mutation hypothesis is based on X-chromosomal inactivation analysis, showing that almost all human pituitary adenomas are monoclonal.[1] However, specific mutations underlying prolactinomas remain to be established, with the exception of genetic syndromes such as MEN 1 syndrome, which is also associated with an increased prevalence of prolactinomas.

CLINICAL PRESENTATION OF PROLACTINOMAS

Prolactinomas cause gonadal and sexual dysfunction related to hyperprolactinaemia, and symptoms related to tumour expansion. Hyperprolactinaemia causes hypogonadotropic hypogonadism in both men and women due to inhibitory effect of increased prolactin concentrations on hypothalamic gonadotropin-releasing hormone (GnRH) release. Consequently, the most common symptoms of hyperprolactinaemia in premenopausal women are amenorrhoea and galactorrhoea. Amenorrhoea is often detected after discontinuation of the use of oral contraceptives (post-pill amenorrhea) or after pregnancy. In men, the symptoms are impotence, decreased libido and decreased beard growth. Unlike in women, gynaecomastia and galactorrhoea are uncommon in men. In some cases, prolactinomas are found as incidentalomas.[9,10]

Prolactinomas are classified according to their diameter in microprolactinomas (<10 mm in diameter), macroprolactinomas (≥10 mm in diameter), and giant prolactinomas (>40 mm in diameter).

Macroprolactinomas typically present with prolactin concentrations that exceed 200 µg/l and symptoms related to tumour expansion, such as headache, visual disturbances, and/or cranial nerve dysfunction. A discrepancy between a large pituitary adenoma and only mildly elevated prolactin concentrations may be due to either pituitary stalk compression by suprasellar extension of a nonfunctioning macroadenoma or a 'high-dose hook effect' of the assay for prolactin. This analytical artefact causes falsely low prolactin determination due to insufficient antibody-prolactin binding in the immunoassay. The correct prolactin concentration will be obtained after appropriate dilution of the serum. Underestimation of actual prolactin concentrations may lead to the erroneous diagnosis of a nonfunctioning macroadenoma instead of a macroprolactinoma. This distinction is of major clinical relevance because a nonfunctioning macroadenoma with visual field defects requires transsphenoidal surgery, whereas the primary treatment of a macroprolactinoma is a dopamine agonist. Therefore, in case of a macroadenoma with only mildly elevated prolactin concentrations, serial dilution of the serum samples should be performed to exclude the presence of this high-dose hook effect of the prolactin assay.

At presentation, patients with microprolactinomas do not have pituitary deficiencies, except for suppressed gonadotrophin concentrations, or visual field defects.[11,12] In patients with macroprolactinomas, hypopituitarism, other than hypogonadism, is present in ~45% of the patients.[11-14] Suprasellar extension of the adenoma often compresses the optic chiasm and classically results in bitemporal hemianopia and diminished visual acuity. Visual field defects are present in ~35% of the patients with macroprolactinomas.[11-13,15,16] In accordance with the higher prevalence of hypopituitarism in men, visual field defects are slightly more prevalent in men compared with women.[11]

TREATMENT OF PROLACTINOMAS

The therapy of prolactinomas is aimed at: 1) reduction of prolactin concentrations and its clinical consequences, such as gonadal dysfunction, infertility, and osteoporosis; 2) reduction of tumour mass, thereby relieving visual field defects and hypopituitarism; 3) preservation of residual pituitary function; 4) prevention of continuing growth of tumour mass, and 5) improvement of quality of life. Treatment goals are similar for micro- and macroprolactinomas, although in the case of macroprolactinomas more emphasis of the therapy is focussed on control of tumour size.

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 tumour volume. The most commonly used dopamine agonists are the ergot-derived dopamine agonists bromocriptine and cabergoline, and the non-ergot derived dopamine agonist quinagolide. Dopamine agonists have a wide spectrum of pharmacological actions at different receptor sites.[17] Therefore, it is not surprising that these drugs display a number of side effects. Dopamine inhibits prolactin secretion through D2 dopamine receptors, expressed by both normal and tumorus pituitary lactotrophs.

Almost 35 years ago, bromocriptine was introduced into clinical practice as the first medical treatment for prolactinomas.[18] It has a relatively short elimination half-life and dosages range from 2.5 to 15 mg, three times daily. For microprolactinomas, bromocriptine normalises prolactin concentrations, restores gonadal function, and induces tumour shrinkage in 60 to 80% of the patients.[13,19,20] For macroprolactinomas, bromocriptine is effective in only 50 to 70% of patients.[13,21,22] Disadvantages of bromocriptine treatment are the frequent occurrence of side effects, leading to interruption of therapy in 12% of the patients.[19,23] Tumour regrowth after discontinuation has been reported, although data on this issue are scarce.[24]

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 concentrations (in 70 to 100% of the patients with microprolactinomas, and in 67 to 88% of the patients with macroprolactinomas), fertility, and to induce tumour shrinkage (in 55% of the patients with microprolactinomas, and in 75% of the patients with macroprolactinomas).[25-31] Therefore, quinagolide seems to be slightly more effective than bromocriptine, and it is associated with less side effects than bromocriptine.[25,27]

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 dose is 0.25 to 0.5 mg twice a week. In microprolactinomas, the average dose is 0.5 mg/week, and in macroprolactinomas 1 mg/week. Several studies have demonstrated the efficacy of cabergoline in normalising prolactin concentrations, and in inducing tumour shrinkage, especially in microprolactinomas. Normalisation of prolactin concentrations are achieved in 75 to 90% of the patients with micro- or macroprolactinomas, and an average decrease in tumour volume of 72 to 92% is reported.[12,15,16,19,32,33] Even in patients with resistance to other dopamine agonists, cabergoline has proven to be effective.[15] Furthermore,

cabergoline seems to induce much fewer and less severe side effects than other dopamine agonists, since only 4% of the patients had to discontinue treatment.[16,19]

Surgical treatment of prolactinomas

In some patients medical treatment does not result in adequate control of micro- and macroprolactinomas. This is mostly due to intolerance to dopamine agonists. In some patients, there may be resistance to the effects of dopamine agonists. In these patients, surgery is mandatory.

Success rates of transsphenoidal surgery differ between micro- and macroprolactinomas. Furthermore, surgical success rates are highly dependent upon the experience of the neurosurgeon.[34] For microprolactinomas, surgery initially restores prolactin concentrations in 85 to 90%.[35-39] For macroprolactinomas, initial surgical remission rates, i.e. normoprolactinaemia, vary between 18 and 80%.[36,38-40] Especially in those macroprolactinomas with parasellar extension, transsphenoidal surgery alone is not curative. A review by Gillam *et al.*, which combined the data from 45 series (n=2137) of microprolactinomas, and 39 series (n=2226) of macroprolactinomas, initially reported remission rates of 75% and of only 34%, respectively.[24] From the same series, long-term recurrence rates were reported of 18% for microprolactinomas, and 23% for macroprolactinomas. Prolactin concentrations, measured one day after surgery, predicted long-term cure.[41]

An adverse effect of transsphenoidal surgery is the induction of hypopituitarism which is more likely to occur after surgery for macroprolactinomas compared with microprolactinomas. The overall mortality rate following transsphenoidal surgery is less than 0.5%.[38,39]

Postoperative radiotherapy of prolactinomas

The role of radiotherapy is limited in the treatment of prolactinomas. In most cases, radiotherapy is applied after unsuccessful transsphenoidal surgery or, rarely, after medical therapy alone. Therefore, in general it is considered a third-line therapy after failure of medical and surgical treatment. In series of patients with unsuccessful transsphenoidal surgery, conventional, fractionated radiotherapy normalised prolactin concentrations in ~34%.[24] Hypopituitarism can be induced by both surgery and radiotherapy, with a cumulative risk after postoperative radiotherapy of ~50% at 10 to 20 years.[42,43]

In conclusion, the efficacy of medical therapy, especially of cabergoline, has limited the indication for surgery. Surgery is reserved for patients with intolerance and/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.

LONG-TERM OUTCOME OF TREATMENT OF PROLACTINOMAS

Remission after withdrawal of dopamine agonists

Withdrawal of bromocriptine or quinagolide results in recurrence of hyperprolactinaemia in almost all patients.[25,44-46] In the past 10 to 15 years, wide variations in remission rates have been reported after withdrawal of cabergoline, with a range of 10 to 70%.[14,25.32,46-48] Colao *et al.* evaluated withdrawal of cabergoline (median duration of therapy 36 to 48 months) in 200 patients with nontumoural hyperprolactinaemia (n=25), microprolactinomas (n=105), and macroprolactinomas (n=70).[14] Recurrence rates of hyperprolactinaemia after a median follow-up of 12 to 18 months were 24% in nontumoural hyperprolactinaemia, 30% in microprolactinomas, and 36% in patients with macroprolactinomas. In this prospective study, normal prolactin concentrations and tumour shrinkage of 50% or more on MRI were stringent conditions before cabergoline withdrawal, indicating that, at least in a subset of patients, dopamine agonists can be withdrawn successfully. This has led to novel guidelines for the treatment and withdrawal of dopamine agonists in patients with prolactinoma.[49] A recent study in a limited number of patients that followed these guidelines reported a recurrence of over ~60% by 18 months.[50] Recently, we performed a meta-analysis on the effects of withdrawal of dopamine agonists in prolactinomas, which included 19 studies with a total of 743 patients. This meta-analysis showed that only 21% of the patients had persisting normopolactinaemia after dopamine agonist withdrawal.[51] Only treatment duration was correlated with treatment success.

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

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 dose, but can be minimised by introducing the drug in a low dose at bedtime. The most common gastrointestinal 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 reversible when the drug is discontinued.[24] Mood alterations, such as anxiety and depression, occur frequently during treatment with dopamine agonists. These psychological side effects are often subtle and therefore difficult to detect.

The dopamine agonists pergolide, bromocriptine, and recently cabergoline, have been associated with increased risk of cardiac valve regurgitation in patients with Parkinson's disease and to induce retroperitoneal and pulmonary fibrosis.[52-63] However, these adverse effects appear to be dose-dependent, and the dose used for the treatment of prolactinomas is approximately ten times lower compared with the dose used for the treatment of Parkinson's disease. At present, eight observational studies on the relationship between cabergoline and cardiac valve regurgitation in prolactinoma patients have been published so far and are summarised in *table 1*.[64-71] Overall, five of these eight studies did not report a significant association between treatment with cabergoline and prevalence of cardiac valve regurgitation, whereas two studies reported an increased prevalence of mild, but not clinically relevant, tricuspid regurgitation and only one study showed an increased prevalence of moderate tricuspid regurgitation (*table 1*). Furthermore, only one study demonstrated a correlation between clinically significant moderate tricuspid regurgitation and the cumulative dose of cabergoline.[68] Single studies reported increased prevalence of morphological changes of cardiac valves, including thickening and calcification,[66] or increased mitral tenting area.[64] Recently, a meta-analysis including six of the above-mentioned studies with a total of 393 patients treated with cabergoline for hyperprolactinaemia showed a significant increased risk of mild plus moderate tricuspid valve regurgitation.[72]

In conclusion, it seems that the risk for valvulopathy in patients treated with dopamine agonists for prolactinoma is low. An increased risk of cardiac valvulopathy should be considered in patients requiring higher doses or long duration of therapy with dopamine agonists. Hence, none of the patients with clinically significant regurgitation had symptoms of cardiac valve disease and the regurgitation was revealed only by systematic echocardiographic evaluation. Therefore, echocardiography should be performed on a regular basis in patients treated with ergot-derived dopamine agonists for prolactinoma until long-term follow-up studies have shown that there is no increased risk after longer duration of treatment than that has been evaluated at present.

Resistance to dopamine agonists

Varying definitions of dopamine agonist resistance are used. Molitch has proposed to use a uniform definition, defining dopamine agonist resistance related to prolactin concentrations as the failure to achieve normoprolactinaemia, and with respect to tumour size as the failure to achieve tumour size reduction of 50%.[73] The prevalence of resistance of prolactinomas to dopamine agonists differs between specific dopamine agonists, macro- or microprolactinomas, and between naive and previously treated prolactinomas. Overall, resistance with respect to normalisation of prolactin concentration and tumour shrinkage can be expected in 25 to 50% of patients taking bromocriptine, and in 5 to 15% taking cabergoline.[73]

Table 1. *Cabergoline and cardiac valve disease in patients treated for prolactinoma*

Author, year of publication (ref.)	No. of patients	No. of controls	Gender (F/M)	Mean age (yr)	Mean cumulative cabergoline dose (mg)	Mean cabergoline duration (months)	Clinically relevant regurgitation	Valvular thickening/ calcification	Mitral tenting area
Lancellotti, 2008[64]	102	51	73/29	51	204*	79*	NS	NS	Sign. increased
Vallette, 2008[65]	70	70	37/33	44	282	55	NS	NS	NA
Kars, 2008[66]	47	78	34/13	46	363	62	NS	Significantly more MV and AV calcification Significantly more TV thickening	NA
Wakil, 2008[67]	44	566	32/12	42	311	45	NS	NS	NA
Colao, 2008[68]	50	50	44/6	37	414	NA	Significantly more moderate TR	NS	NA
Bogazzi, 2008[69]	100	100	79/21	41	279	67	NS	NA	NA
Herring, 2009[70]	50	50	20/30	51	443	792	NS	NS	NS
Nachtigall, 2009[71]	100	100	52/48	44	253	48	NS	NA	NA

NA = not available; NS = non significant; TR = tricuspid regurgitation; MV = mitral valve; AV = aortic valve; TV = tricuspid valve. * Median.

Possible treatment options for patients with dopamine agonist resistance are to increase the dosage or to switch to another dopamine agonist, or transsphenoidal surgery.

Pregnancy

Two major issues arise in the treatment of prolactinomas and pregnancy: 1) effect of pregnancy on prolactinomas, and the possibility of growth of prolactinomas; 2) effect of dopamine agonists on foetal development.

During normal pregnancy, oestrogens stimulate prolactin synthesis and secretion, and promote lactotroph cell hyperplasia. Throughout normal pregnancies, there is an increase in pituitary volume up to 136%, beginning in the second month of gestation.[74] After delivery, the pituitary rapidly involutes and returns to its normal size by six months postpartum. According to data collected by Gillam *et al.*, five studies have reported data on the risk of symptomatic tumour enlargement in pregnant women with prolactinomas.[24] These data indicate that the risk of detectable tumour enlargement is only 3% (12 of 457 pregnancies) for microprolactinomas, but as high as 32% (45 of 142 pregnancies) for macroprolactinomas not previously operated. Surgical intervention was necessary in 12 of these 142 cases (8%). In five patients with microprolactinomas and 17 patients with macroprolactinomas, dopamine agonist bromocriptine was reinstituted.

Most women diagnosed with prolactinomas will require treatment of hyperprolactinaemia for restoration of fertility. Therefore, it is likely that the foetus will be exposed to dopamine agonists, at least for the initial three to four weeks of gestation. Moreover, all dopamine agonists have been shown to cross the placenta in humans. The use of bromocriptine, however, taken in the first 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).[24] Childhood development was analysed in 64 of these children, without adverse effects.

Considerably fewer data are 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.[23] 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 incidence of spontaneous abortion, premature delivery, or congenital malformations.[24] Recently, Colao *et al.* reported data of 329 pregnancies in women during the use of cabergoline.[75] Spontaneous abortions occurred in 9%, and there were eight cases of stillbirths (3%), and 23 cases of neonatal major and minor abnormalities (7%). The incidence of spontaneous abortion in the general European population is approximately 11%.[76] Major neonatal abnormalities are estimated at 6% worldwide.[75]

The follow-up of women with microprolactinomas during pregnancy includes withdrawal of dopamine agonists at the moment pregnancy is established. Periodic assessment of prolactin concentrations 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 tumour enlargement. Therefore, visual field testing and/or MRI should be assessed when symptoms of mass effects, such as headache or visual disturbances, occur. If tumour enlargement is confirmed, reinstitution of the dopamine agonist bromocriptine is often sufficient to reduce size. However, persistent visual field defects may necessitate transsphenoidal surgery. In women with macroprolactinomas, the decision to continue or withdraw dopamine agonist treatment should be made on an individual basis, taking into consideration the extent of para-/suprasellar extension of the macroprolactinoma and its relation with optic chiasm/nerves. Furthermore, careful follow-up with visual field testing is advisable. MR imaging is reserved for those patients with symptoms of tumour enlargement and/or progressive or new visual field defects. Again, if tumour enlargement is confirmed, reinstitution of the dopamine agonist bromocriptine is preferred to surgery, and transsphenoidal surgery is reserved for women who do not respond to bromocriptine and in whom progressive deterioration of visual fields is documented despite bromocriptine therapy.

In conclusion, growth of prolactinomas during pregnancy is due to the withdrawal of dopamine agonists and stimulatory effects of high oestrogen concentrations. Bromocriptine is the therapy of choice to treat hyperprolactinaemia in order to restore fertility, and can be safely withdrawn in women with microprolactinomas when pregnancy is confirmed. Careful monitoring is warranted for women with macroprolactinomas during pregnancy. For women who are intolerant to bromocriptine, cabergoline is a reasonable second choice.

Bone mineral density

Patients with prolactinomas are susceptible to develop osteopenia and osteoporosis. Prolactinoma-related bone loss is related to the duration of secondary hypogonadism before the diagnosis of prolactinoma is established and treatment is instituted. Prolactinomas are more prevalent at young age, and, therefore, peak bone mass may 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 using dual energy X-ray

absorptiometry) below the expected range for age at one or more sites.[77] Furthermore, in 15% of men with prolactinomas osteoporosis of the lumbar spine was present.[78] In most men and women with hyperprolactinaemia, bone loss is reversed, or at least interrupted, once prolactin concentrations and gonadotropins are normalised. This indicates the importance of adequate disease control, i.e. normoprolactinaemia, to prevent long-term complications.

Quality of life

Endocrine diseases have clear psychological implications.[79] Furthermore, despite normalisation 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.[80] Assessment of functional and mental well-being has become an important outcome of long-term follow-up in pituitary adenomas. Quality of life, measured with self-reported health parameters, is decreased in patients with pituitary adenomas.[81-90] In women treated for microprolactinomas, quality of life is impaired, especially due to increased anxiety and depression.[91,92]

Malignant prolactinoma

The incidence of pituitary carcinomas is extremely low.[93] Until recently, only ~140 cases with pituitary carcinomas have been reported, one-third of these being malignant prolactinomas.[94,95] 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 concentrations. Furthermore, histological parameters, such as proliferative Ki-67 index and p53 immunoreactivity, are correlated with biological behaviour of pituitary adenomas.[93,96] It is postulated that pituitary carcinomas arise from the transformation of initially large, but benign adenomas.[93] 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.[96] Once metastatic disease is established, treatment modalities are surgery, radiotherapy, and chemotherapy. In some patients, treatment with octreotide is an option. If tolerated, dopamine agonists should be continued.

CONCLUSION

Prolactinomas are the most prevalent pituitary adenomas. Dopamine agonists are the first-line of treatment for prolactinoma, capable of effectively relieving symptoms, normalising prolactin concentrations and reducing tumour size in most cases. Recurrence of the disease after withdrawal of dopamine agonists occurs in a considerable proportion of patients, and therefore follow-up after withdrawal is necessary. The probability of persisting normoprolactinaemia after withdrawal is highest when tumour volume has reduced by 50% or more, and normoprolactinaemia has remained stable even after tapering the dose. Follow-up of prolactinomas also requires assessment of bone mineral density and attention to quality of life. Although dopamine agonist treatment appears safe in most patients treated for prolactinoma, evaluation of cardiac valvulopathy should be considered in patients treated with ergot-derived dopamine agonists, with repetitive echocardiography in those treated with a relative high dose and/or long duration of bromocriptine or cabergoline. Additional treatment with transsphenoidal pituitary surgery and/or radiotherapy should be reserved for patients with intolerance or resistance to dopamine agonists, since these secondary therapies have a high risk of developing hypopituitarism.

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