Macroprolactinomas: Retrospective follow up study in the MR imaging and correlation with clinical symptomatology

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Abstract

OBJECTIVES: Retrospective follow-up study on patients suffering from macroprolactinomas which were treated with agonists of D2 receptors; the MRI results were correlated with the clinical symptomatology and with the level of prolactin in the blood.

METHODS: From 1996 to 2006 we followed 38 patients diagnosed with macroprolactinoma. All patients underwent MRI in same protocol two times. The indication for MRI was based on the clinical symptomatology (signs of hormonal dysfunction, visual fields impairment) or increased blood level of prolactin.

RESULTS: The first predominant clinical signs in males were local manifestations of expansive process and in women hormonal dysfunction. Intratumorous haemorrhage in patients undergoing the treatment with the agonists of D2 receptors is common, it was encountered in 25 cases, but only in two cases it was followed by a more serious clinical symptomatology, which had to be referred to the department of the neurosurgery. Even when there were pronounced regressions or near complete disappearance of the tumour and normalisation of the blood level of prolactin, withdrawal of the treatment with agonists of D2 receptors caused increase in size of the adenoma and increase of level of prolactinaemia.

CONCLUSION: Only two patients presented with serious clinical symptomatology associated with intratumoral hemorrhage. The hemorrhages are more common during the first weeks of therapy, but can happen at any time thought out the treatment with D2 receptor agonists. Our hypothesis: the prolactinomas with higher level of prolactin have greater tendency for larger hemorrhages.

ORIGINAL ARTICLE

INTRODUCTION

Magnetic resonance imaging (MRI) is the modality of choice to investigate suspected sellar region pathology. It provides by far the largest amount of information related to the sella turcica area lesions. In large percentage of cases it can even approximate the underlying pathology with great accuracy [1]. Other investigating modalities are useful as well. Computed tomography (CT) is used to determine presence of calcifications and erosive changes on surrounding bony structures or angiography to determine vascular nature of the pathology, such as aneurysm [2].

By definition macroadenomas are adenomas which exceed 1 cm in size [3]. Sellar macroadenoma presents certain characteristic features on MRI, such as balloon-like enlargement of sella turcica, non-invasive growth, lobulated shape, extension into the supra-sellar and para-sellar (cavernous sinus) regions, enhancement on contrast MRI sequences and absence of calcifications, however, all these features can be observed, significantly less often, in other pathologies involving sellar region.

Macro-prolactinomas show characteristic signal features on MRI. On T1W sequence they present slightly increased or isotense signal, they have slightly increased signal on T2W sequence and moderately enhance on contrast sequence, in comparison with normal tissue of the pituitary gland. From all macroadenomas slightly more the 50% are endocrinologically active, from these approximately half are macro-prolactinomas [4,5].

Diagnosis of macro-prolactinoma can be established based on clinical symptoms such as galactorhea, amenorrhea, loss of libido, laboratory investigation such as blood level of prolactin and radiological imaging methods, primarily MRI. Accurate diagnosis with possibility of continuous MRI monitoring and the discovery of D2 antagonists led to marked reduction in the number of patients requiring neurosurgical intervention or gamma knife treatment [6,7,8].

MRI during the treatment of macroprolactinomas with agonists of D2 receptors can show not only the reduction in size of the expanding lesion, but also destructive changes within the lesion, such as hemorrhages which are not rare and can be observed even before the onset of the therapy with D2 receptor agonists [9, 10, 11].

We are presenting our experience with the diagnosis and clinical follow up of our group of patients being diagnosed with macroprolactinoma.

PATIENTS AND METHODS

From 1996 to 2006 we followed 38 patients diagnosed with macroprolactinoma; 21 were males and 17 women. Mean age was 34.4±11.2 years. All patients underwent MRI on Gyroscan Phillips 1.5 T system with the following protocol: axial T2 weighted image with slice thickness (THK) 6.0/0.6 mm through out the whole head, with parameters: repetition time (TR) 4 420 ms, time to echo (TE) 100 ms, flip angle (FA) 90°, followed by sagital; and coronal T1 weighted image (with parameters: TR 550 ms, TE 15 ms, FA 90°), and T2 weighted image (with parameters: TR 3 000 ms, TE 120 ms, FA 90°) centered to the sellar region with THK 3.0/0.3 mm. The sagital and coronal images centered to the sellar region were repeated after administration of Gd-DTPA (the dose 0.1 mmol/kg).

In 8 patients the treatment with D2 receptor agonists was started before the first MRI study. Three of these patients underwent CT imaging before the initiation of the treatment. After the first MRI the second, control study, was done in a period ranging from 1 week to 23 months. The indication for MRI was based on the clinical symptomatology such as signs of hormonal dysfunction, visual fields impairment or laboratory findings such as increased blood level of prolactin. Increased blood level of prolactin was in the range from 90 μg/l to 4780 μg/l (Normal blood level of prolactin in our laboratory is in between 3.6 μg/l to 13.4 μg/l for females and 2.8 μg/l to 7.2 μg/l for males). Patients were treated with bromocryptin, cabergolin or tergurid.

RESULTS

Table 1 lists first clinical signs which raised suspicion of prolactinoma. If the patient complained of two different symptoms, we listed both. Visual symptoms are listed globally; in some instances it was disturbance of perimeter which often prevailed, in other instances it was a loss of visual acuity. Often both these symptoms were present simultaneously and it was impossible to separate them and determine which one preceded.

Eight patients underwent the first MRI study while being on D2 agonist therapy; from whose five (63%) were diagnosed with intra-tumoral hemorrhage. In the group of thirty patients who were not treated with D2 agonists prior to MRI, the intra-tumoral hemorrhage was seen in only three patients (10%) as illustrate Figure 1 and 2; following the D2 agonist therapy the intra-tumoral hemorrhage was seen in additional 17 (57%) patients. These hemorrhages were clinically asymptomatic in 63% of patients. In reminder of the patients the clinical symptoms of hemorrhage lasted only few days (headaches, nausea, vomiting). Two patients presented with visual impairment (narrowing of visual fields and decreased visual acuity), but without any other symptoms of intra-tumoral hemorrhage; these patients had to be referred for trans-sphenoidal neurosurgical intervention. Post surgery both patients gradually improved.

In three patients the treatment with D2 receptor agonists failed. These patients experienced high levels of prolactin with significant clinical signs and required neurosurgical intervention as illustrates Figure 3. In five patients we observed deterioration of visual perimeter or visual acuity while on D2 receptor agonist treatment which was most likely to the presence of residuum or relapse of macroadenoma. The patients, on imaging

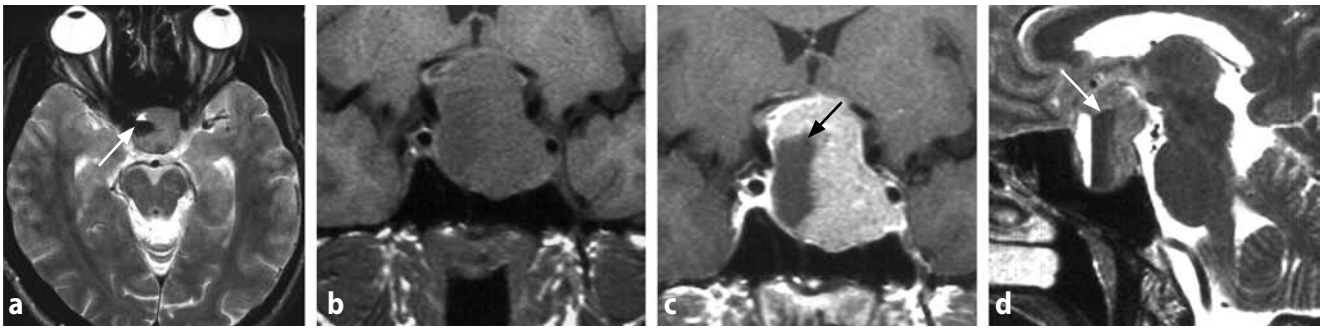

Figure 1. Transversal slice T2 weighted image (T2WI) (a), coronal slice T1WI (b) and after administration Gd-DTPA (c) and sagital slice T2WI (d). A 35-year-old man, the first examination before treatment, adenoma extending superiorly into suprasellar cistern and laterally into left cavernosus sinus, in ventrolateral part there was acute hemorrhage (black arrow).

studies, proved to have deformities or deviations of optic chiasm or optic pathways. This was probably caused by formation of adhesions between the retracting adenoma and supra-sellar structures (so called suprasellar arachnoiditis). In two patients there was an empty sella turcica. In this group of patients the MRI was performed based on suspicion of tumor growth.

The blood level of prolactin did not correlate with the decrease in size of the adenoma. Often very small residual adenoma produced large quantities of prolactin blood level.

In three patients with discrete imaging findings or with "complete" disappearance of the adenoma on MRI and normalization of prolactin blood levels we discontinued therapy with D2 receptor agonists, as illustrates Figure 4. In these patients what followed was an increase blood level of prolactin and reappearance of the adenoma on MRI.

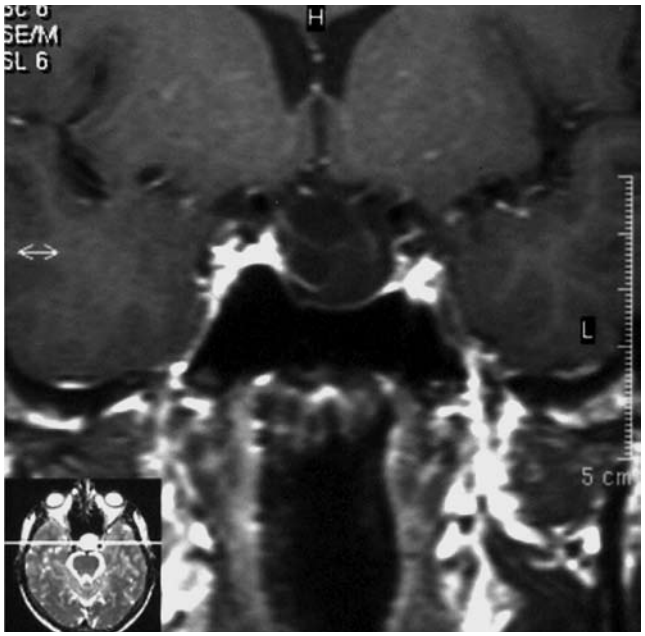

Figure 2. Coronal slice T1WI-Gd-DTPA, the same patient as in Figure 1, after 28 months treatment with agonists of D2 receptors. Invagination of suprasellar cisterns, partially empty sella.

DISCUSSION

From 38 patients with macroprolactinomas, in whom we repeated MRI, 21 were males and 17 females. This supports the frequently observed fact that while microprolactinomas are more frequent in women, macroprolactinomas are more frequent in males. In males the local expanding phenomenon is the leading clinical symptom rather then the hormonal dysfunction (See Table 1.) The clinical symptoms caused by an increased blood level of prolactin (galactorhea, amenorrhea) prevail in females. This is caused by more conspicuous manifestation of hormonal dysfunction in women, being difficult to distinguish what was the primary symptom; galactorhea or amenorrhea. Quite often they both present simultaneously.

Corsello *et al.* [11] treated patients with giant invasive macroprolactinomas with Caberolin having excellent therapeutic results; the size of macroprolactinomas invariably decreased and the blood level of prolactin normalized. Liu *et al.* [7] reported positive therapeutic effect of D2 receptor agonists in 90% of their patients. In the case of drug intolerance or drug ineffectiveness they recommend transphenoidal neurosurgical removal well tolerated in their group of patients. Vance *et al.* [12] emphasized multidisciplinary approach by ophthalmologist, endocrinologist and neurosurgeon in treatment of pituitary adenomas.

Ostrov et.al [13] proposed to classify macroprolactinomas as solid, hemorrhagic and with increased contents of water, based on MRI characteristics. We also observed foci of increased signal in T2 weighted image being of decreased signal on T1 weighted image, corresponding to the water contents. In our opinion these changes are due to the destruction of the tumor, often combine in one patient and don't have any significance for further treatment.

Increased signal on T1 weighted image within the tumor can be sign of early hemorrhage (methemoglobin), increased presence of cholesterol, presence of melanin or presence of fat after surgical intervention. Increased signal on T1 and T2 weighted image are due to the early hemorrhage or cholesterol cyst in craniopharyngeoma. This is the reason why our MR protocol includes T1

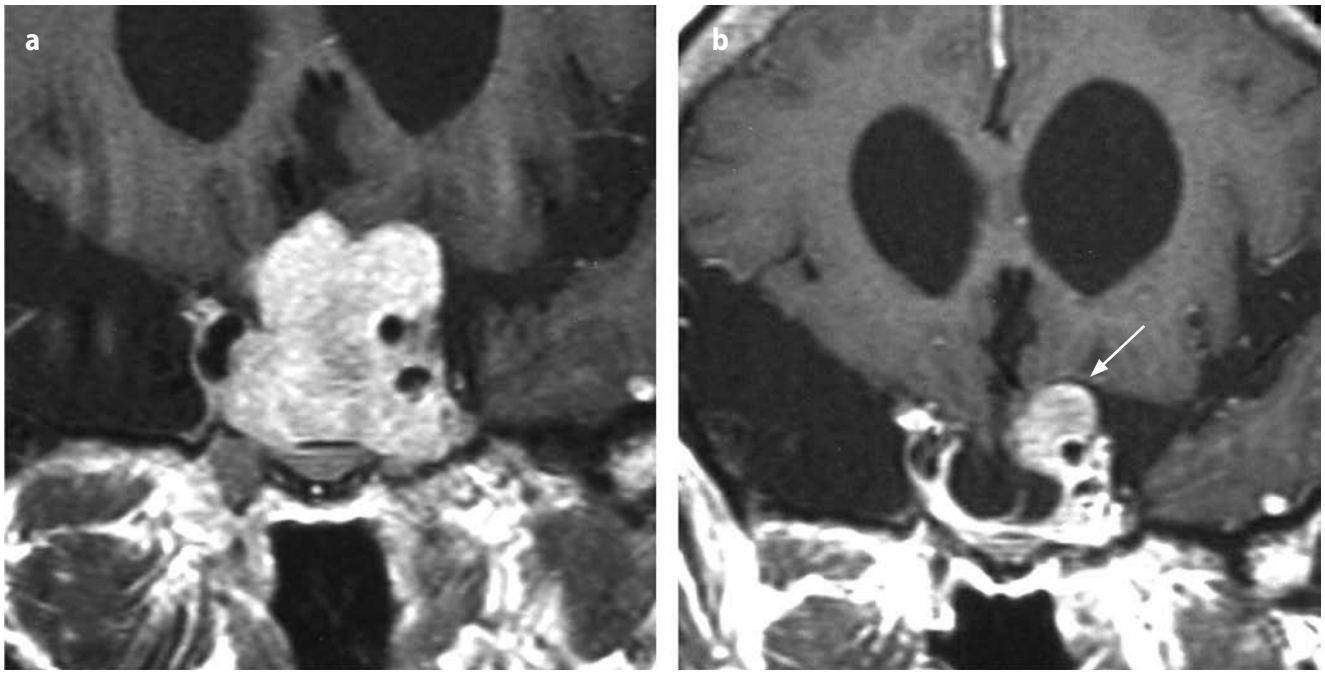

Figure 3 a, b. Coronal slice T1WI-Gd-DTPA, a 50 year-old women with hyperprolactinemia. Adenoma extending superiorly into suprasellar cistern and laterally into cavernosus sinus bilaterally (a). Coronal slice T1WI-Gd-DTPA, the same patient, after 5 months treatment with agonists of D2 receptors. Decrease in size of adenoma, residuum suprasellar on the left (black arrow), invagination of suprasellar cisterns (b).

Table 1. The first symptoms in patients with macroprolactinomas.

Clinical features	Male n=21	Female n=17	Overall n=38
Galactorhea	1 (5%)	12 (71%)	13 (34%)
Amenorhea		12 (71%)	12 (32%)
Visual impairment	15 (71%)	2 (12%)	17 (45%)
Non-specific symptoms (headache)	5 (24%)	3 (18%)	8 (21%)

and T2 weighted image before and T1 weighted image after contrast injection (Gd-DTPA). Occasionally it is necessary to repeat MRI with time delay; on T2 weighted image there can be decrease in signal intensity due to the conversion of methemoglobin to ferritin.

The follow-up MRI was performed at various time intervals depending on the clinical symptomatology and blood levels of prolactin. The treatment with D2 receptor agonists decreases the intra-cellular level of cAMP which leads to suppression of prolactin secretion. The regression of the size of the tumor is related to the decrease in size of the lactotropic cells caused by involution of endoplasmatic reticulum and Golgy apparatus [13] and to the anti-mitotic effect of the dopaminoergic agonists [14,15].

Immediately after the onset of therapy with D2 receptor agonists vascular thromboses, infarctions and hemorrhages within the adenomas become apparent. According to the literature [16,17,18] there is no necrosis of lactotropic cells. This becomes evident after prolong time of therapy.

Success of conservative therapy is reflected by decreasing size of the macroadenoma, however, the most important are the levels of blood prolactin. If these normalize even the fairly large residuum of adenoma is not of major importance with one exception: the secure distance from other intracranial structures, mainly from hypothalamus and optic pathways. In our judgment the secure distance is 2 to 3 mm having in mind the eventual use of gamma knife. In our experience the residual size of the adenoma was seldom in correlation with blood levels of prolactin.

It is assumed that the agonists of D2 receptors cause involution rather then necrosis of the cellular component of the lactotropic cells. This was also confirmed by our observation that the discontinuation of treatment with D2 receptor agonists leads to increase in size of the "disappeared" adenoma and increase of blood levels of prolactin. From the MRI it is not always easy to distinguish between the residuum of adenoma and residuum of normal pituitary gland tissue.

It is frequently argued that the treatment with D2 receptor agonists increases the frequency of hemorrhage into the marcroprolactionoma. Yousem *et al.* [19] found intratumoral hemorrhages in 13% of patients before and in 45% of patients after the treatment. Other authors had similar experience [9,13]. In our study only two patients presented with serious clinical symptomatology associated with intratumoral hemorrhage. These hemorrhages are more common during the first weeks of therapy, but can happen at any time thought out the treatment with D2 receptor agonists [19]. The hemorrhage is often decreasing in size in weeks; this is due to the resorption of the hematoma. In our judgment – not confirmed statisti-

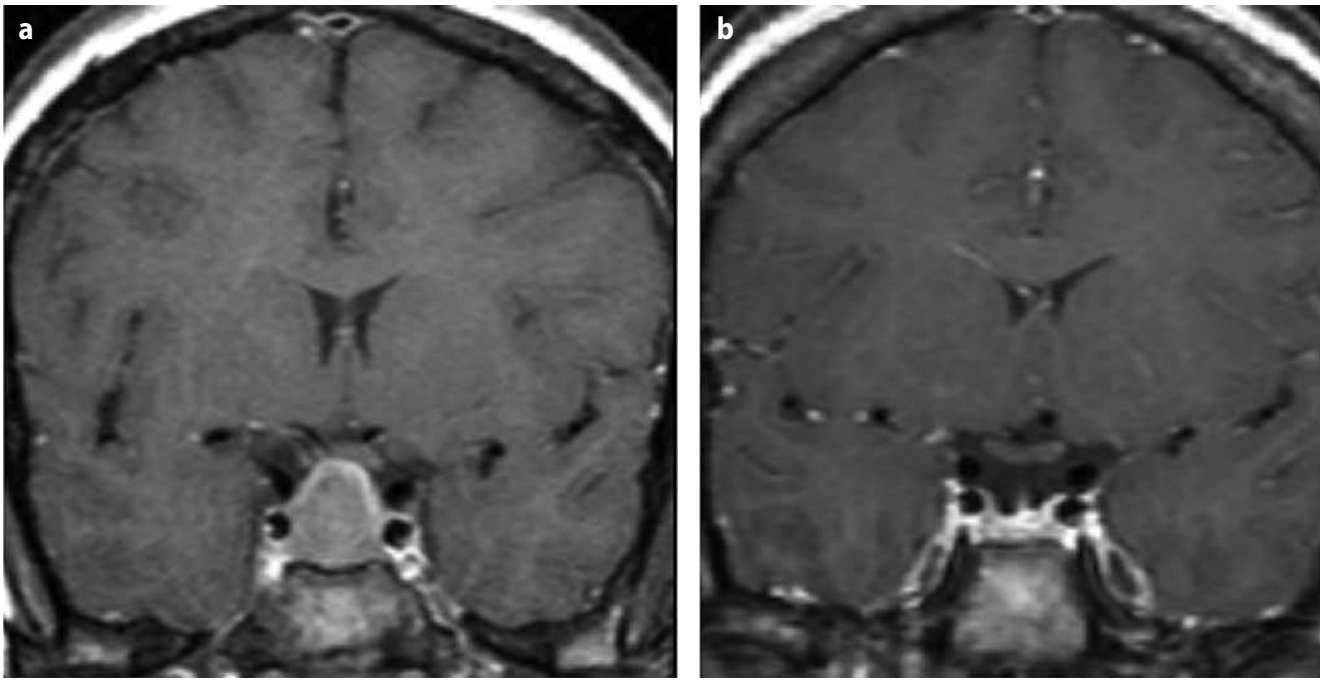

Figure 4 a, b. Coronal slice T1WI-Gd-DTPA, a 24-year-old man with suspicion of macroprolactinoma, intrasellar expansion with suprasellar propagation (a). Coronal slice T1WI-Gd-DTPA, the same patient after 13 months treatment with the agonists of D2 receptors. Macroadenoma was substantially decreased in size (b).

cally – the prolactinomas with higher level of prolactin have greater tendency for larger hemorrhages. The need for control MRI is the progression of visual impairment, especially constriction of perimeter and of course to rule out the growth of the tumor. Occasionally we observe invagination of the chiasm and optic nerves into the sellar region which, in our opinion, is caused by adhesions. This is usually in cases with significant destruction of sizable adenoma. These patients are clinically stable and do not need any change in therapy.

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