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Review

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Macroprolactinoma: a diagnostic and therapeutic update

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Summary

Prolactinomas are the most common type of pituitary adenomas. Macroprolactinomas are the name used for these tumors when their size is $\geqslant$1 cm. These tumors commonly cause symptoms due to the excessive production of prolactin as well as complaints caused by tumor mass and compression of neural adjacent structures. Clinical diagnosis and assessment of macroprolactinoma are based on the measurement of serum prolactin concentrations and the morphological evaluation of the pituitary gland by magnetic resonance imaging. Dopamine agonists are the first-line treatment modality, with cabergoline being preferred to bromocriptine, because of its better tolerance and feasibility of administration. Cabergoline therapy has been reported to achieve normalization of prolactin levels and gonadal function and reduction of tumor volume in >50% of patients with macroprolactinoma. Resistance or intolerance to dopamine agonists are the main indications for transsphenoidal adenomectomy in patients with macroprolactinoma. External radiation therapy has been used in patients with poor response to medical and surgical procedures. Clinically significant tumor growth may occur during pregnancy in women with macroprolactinomas, especially if they have not received prior surgical or radiation therapy. Visual fields should be assessed periodically during pregnancy and therapy with dopamine agonists is indicated if symptomatic tumor growth occurs. Cystic and giant prolactinomas as well as the rare cases of malignant prolactinomas have special peculiarities and entail a therapeutic challenge.

Introduction

Prolactinoma is usually a benign tumor that appears as a result of the monoclonal expansion of a cell line of lactotrope cells of the adenohypophysis, probably due to somatic mutations.[1] It is the most common pituitary tumor (~50%) and usually appears in women aged 20–50 years, with a female:male ratio of 10:1 in that period. Its annual incidence is 6–10 cases per million of inhabitants and its prevalence of 60–100 cases per million, although recent studies indicate that the prevalence may be three to five times higher.[2]

More than 90% of prolactinomas are microprolactinomas (<1.0 cm in diameter), whereas the rest are macroprolactinomas ($\geqslant$1.0 cm).[3–6] Macroprolactinomas constitute approximately half of all functioning pituitary macroadenomas.[7] Compared with microprolactinomas, these tumors have a different distribution frequency in the general population and its biological behavior also differs according to the age and sex of the patients. This review focuses on the most updated and relevant clinical, diagnostic and therapeutic aspects of the macroprolactinoma as well as several different special clinical situations related to this type of tumor.

Macroprolactinoma according to age and sex

Children and adolescents

Pituitary adenomas are very uncommon (~3% of all brain tumors) in prepubertal children and, in most cases, they are not functioning pituitary adenomas.[8] Prolactinomas are therefore exceptional in children and its clinical presentation may be different from that of adults. Unlike adults, macroprolactinomas are more common (~60–80%) than microprolactinomas in children and adolescents.[9–12] Furthermore, in this age group, prolactinomas are more aggressive and have increased proliferative capacity that in adults, i.e. they are usually macroprolactinomas, sometimes large, and some occasions manifesting as authentic invasive giant prolactinomas.[8,11–18]

Adults

Prolactinoma in adults occurs more frequently (>70%) in women, mostly in the form of microprolactinoma (female:male ratio, 20:1). On the contrary, macroprolactinoma is more frequently reported in males,[3–7,19] with a macro-/microprolactinoma ratio of ~5:1.[19] Most (~60%) of the adult males with macroprolactinomas are diagnosed before the age of 40 years; mainly in the fourth decade of life, where about one-third of the patients are diagnosed (Figure 1). Although macroprolactinomas are most common in young men, they have also been reported in elderly males, sometimes presenting as authentic giant prolactinomas.[20,21]

Biology and clinical course of prolactinomas seems to be different in men and women. Although initially it was thought that the predominance of macroprolactinomas in males was due to a delay in diagnosis, several studies have shown that this fact could be because males frequently develop tumors with greater mitotic activity and, therefore, increased capacity of proliferation and invasiveness.[22–24]

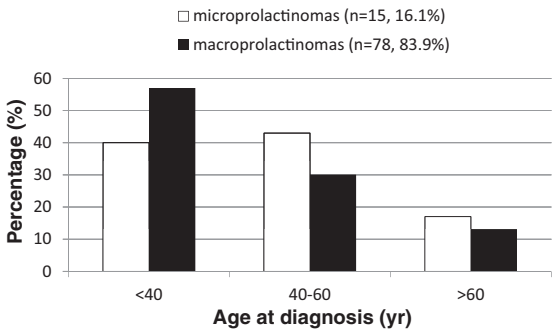


Figure 1. Percentage distribution according to size (micro- and macroprolactinoma) and age at diagnosis in a group of 93 male adults (>18 years) with prolactinomas.

Clinical features

The main complains at diagnosis in males with macroprolactinoma are visual disturbances and headaches, symptoms that are related to the compressive effect of the tumor mass.[4,7,19,25] As it occurs in men with microprolactinomas, the majority of patients (~80%) show symptoms of hypogonadism (erectile dysfunction associated or not to decreased libido) as a result of hyperprolactinemia-induced hypogonadism and compression of the gonadotrope cells by the tumor.[4,26] Partial or total hypopituitarism at diagnosis appears in 78% of males with macroprolactinomas; the gonadal (74%) and somatotropic (31%) axes being the most frequently affected, followed by thyrotropic (25%) and corticotropic (23%) axes.[19] Anemia is frequently (~40–45%) found in men with prolactinomas.[27,28] It is generally a mild normochromic normocytic anemia (hemoglobin >11 g/dl), associated with the presence of secondary hypogonadism or hypopituitarism. Usually, it improves after normalizing serum PRL levels and increasing serum testosterone levels with dopamine agonists (DA)[27] and hormone replacement therapy.[29]

In women, the first clinical signs of macroprolactinomas are more frequently (~70%) related with hormonal dysfunction (amenorrhea and galactorrhea) than with the effect of the tumor mass.[7,30] In children and adolescents, macroprolactinomas present clinically with symptoms derived from tumor growth such as headache and visual disturbances.[9] Moreover, in adolescent women, these symptoms manifest themselves together with primary or secondary amenorrhea. Delayed puberty due to hypogonadotropic hypogonadism induced by hyperprolactinemia or by tumor effect on gonadotropic cells is another manifestation of macroprolactinoma in children.[31] Finally, growth arrest is usually not developed in this population due to the fact that somatotropic axis is generally preserved.[9]

Diagnostic update

Morphological study

Magnetic resonance imaging (MRI) is the method of choice for the morphological study of macroprolactinomas in both initial assessment and follow-up[7] This technique provides information not only on the size of the tumor but also on their relationship with the surrounding brain structures and

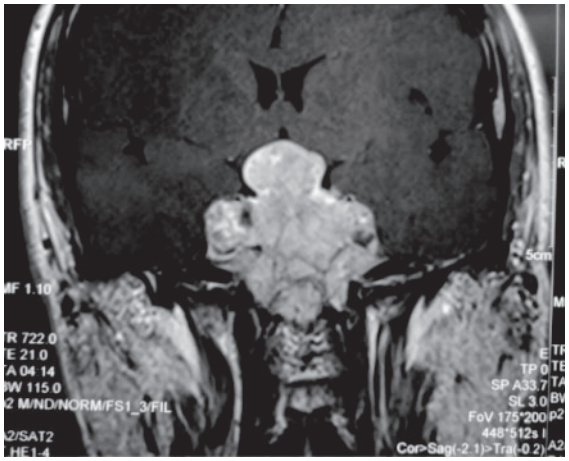


Figure 2. MRI **c**oronal section with a macroprolactinoma showing a hyperintense signal on T1 after the administration of paramagnetic contrast.

neuro-ophthalmological pathways. Also, the findings in the MRI are associated not only with serum PRL concentration but also with clinical symptoms.[7] These tumors show characteristic signs in the MRI; they are isointense or slightly hyperintense on T1-weighted images with an increase in signal compared with normal pituitary tissue after administration of paramagnetic contrast and slightly hyperintense on T2-weighted images[7] (Figure 2). MRI is also useful in the follow-up of patients with macroprolactinomas treated with DA as it shows the reduction of tumor size as well as other alterations that can be associated with chronic medical treatment such as intratumoral hemorrhage, intraselar chiasma and optic nerves invagination and empty sella.[7,19,32,33]

Hormonal diagnosis

The degree of hyperprolactinemia is usually related to the size of prolactinoma.[34] Macroprolactinoma is usually associated with serum PRL levels >250 ng/ml. A serum PRL level >500 ng/ml makes the diagnosis of macroprolactinoma almost certain.[35] Sometimes PRL levels may be normal or slightly elevated in patients bearing macroprolactinomas. This may be due to the 'hook' effect of the PRL, an artifact of the PRL assay that can be observed when serum PRL concentrations are very high and saturate antibodies of the assay giving rise to falsely low results. To avoid this phenomenon, repeating the quantification of PRL in serum samples after dilutions of 1:100 is recommended, particularly in male patients, with a mild–moderate PRL elevation associated with a presumably non-functioning pituitary macroadenoma.[36,37]

Therapeutic update

Medical therapy

The initial treatment of choice of the macroprolactinoma is currently DA.[37–39] This therapy achieves a reduction in the levels of PRL, restoration of the gonadal function and reduction of tumor size in a high percentage of patients (Figure 3). Within this pharmacologic group, cabergoline (CAB) is preferred due to a greater therapeutic efficiency, a better tolerance and therefore, greater adherence to treatment and, finally to a more convenience of administration of the drug.[35,37,38,40,41] A prospective study of 26 patients (15 women and 11 men) with previously untreated macroprolactinomas showed that treatment with CAB (0.25–2.0 mg/week) was followed by normoprolactinemia in 21 patients (81%) and significant reduction in tumor size in 92% of patients after 6 months of treatment.[26] In this study, the therapeutic regimen achieved similar effects in 94.7% and 42.1%, respectively, of patients intolerant to bromocriptine (BRC). Similarly, 19 of 37 patients (51.3%) resistant to BRC and quinagolide achieved normoprolactinemia and 30.3% of them showed a significant reduction in tumor size.[26]

DA are also the drugs of choice in the therapeutic management of macroprolactinomas in men.[4,19,25,42,43] In a 24-month prospective study, treatment with CAB (0.25–3.5 mg/week) normalized PRL levels in 76% of patients, significantly reduced tumor size in all patients with a percentage reduction of the maximum tumor diameter of 84%, normalized serum testosterone in 60% and sperm alterations in the majority (>90%) of patients.[25]

Given the effectiveness and tolerance of the DA, this pharmacologic group, mainly CAB, also constitutes the initial therapy of choice in children and adolescents with macroprolactinomas.[9] These drugs achieve the normoprolactinemia, the restoration of the gonadotropic axis function and the reduction in the tumor size in the majority of patients.[11,12,18]

It has been reported that CAB, even at high doses, does not normalize PRL in ~18% of patients with macroprolactinomas despite reducing the tumor size. CAB doses exceeding 3 mg/week do not seem to offer benefit on the control of the overproduction of PRL.[40]

Although cure of macroprolactinoma after long-term treatment with DA has been reported,[44] complete remission (normoprolactinemia associated with absence of tumor image) is not easy to achieve. A study showed a recurrence rate of hyperprolactinemia in 43.3% of patients with macroprolactinomas after 5 years of CAB withdrawal. In this study,

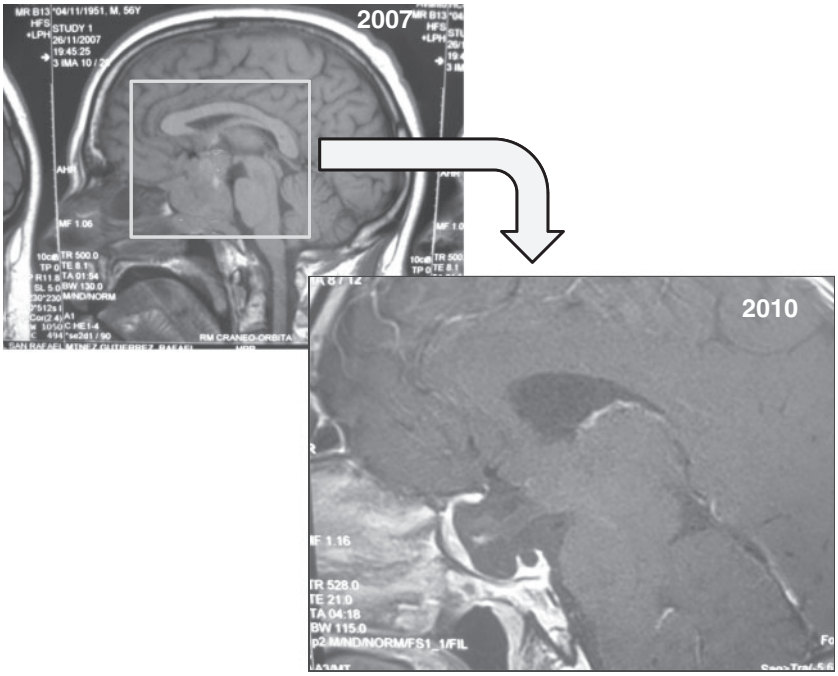


Figure 3. MRI sagittal section that shows the morphological evolution of a macroprolactinoma in a male patient after 3 years of treatment with DA.

tumor recurrence was 77.5% in those patients that had small remnant tumor in MRI at the time of the CAB withdrawal versus 32.6% in those showing no evidence of tumor image at that time.[45] Persistent control of hyperprolactinemia without evidence of tumor growth after 24–96 months of CAB withdrawal has been reported in ~50% patients with macroprolactinoma.[46] Recurrences usually appear in the first year following the withdrawal and one study showed that the risk of recurrence was 18% by millimeter tumor mass remaining before the withdrawal of the CAB.[47] The probability of complete cure is greater when treatment with DA has been prolonged (>2 years) and there is no tumor rest in MRI.[37,48]

Surgical therapy

Surgical treatment of macroprolactinoma is currently considered as second-line therapy after medical treatment with DA.[37] Adenomectomy via transsphenoidal (microscopic or endoscopic) approach is the main surgical technique used in the majority of the macroprolactinomas. Craniotomy is reserved for large tumors inaccessible to conventional procedures.[49] The main surgical treatment indications include resistance, intolerance or lack of adherence to medical treatment, cerebrospinal fistulas secondary to a reduction of tumor size after therapy with DA, neuro-ophthalmologic defects such as rapid loss of vision or cranial pars paralysis due to intratumoral hemorrhage or pituitary apoplexy.[37,39] A surgical series of 148 macroprolactinomas reported by Kreutzler *et al.*[50] was accompanied with initial remission (PRL normalization without pharmacological treatment at least 4 weeks before surgery on day 7 after surgery) in 42.6% of patients with macroprolactinomas with suprasellar extension and in 24.3% in those with parasellar and/or sphenoidal extension. Recurrence rate of hyperprolactinemia was 25.6% and 20%, respectively. In this study, none of the 10 patients with giant prolactinoma showed remission after surgery.

Radiotherapy

Given the excellent response of macroprolactinomas to DA, today the use of external radiotherapy should be reserved for cases of resistance to medical treatment and poor response to surgery and to malignant tumors.[51] Although the addition of radiotherapy to medical treatment and surgery helps to control the tumor size, hyperprolactinemia often persists.[19] The maximum therapeutic effect of radiotherapy requires long time, sometimes 10–20 years. On the other hand, a recent study showed that treatment with radiotherapy in 14 men with macroprolactinomas was associated with hypopituitarism in all cases after 12 years after radiotherapy.[19] Finally, radiation therapy has been linked recently with the development of a giant prolactinoma in a young male, 15 years after its administration after

surgery of a pontine glioma, treated at 6 years of age.[52]

Special situations

Hereditary macroprolactinomas

Familial isolated macroprolactinoma

Prolactinoma is the tumor most often (~40%) observed in familial isolated pituitary adenoma (FIPA) syndrome.[53,54] This disorder occurs when two or more cases of pituitary adenomas appear in the same family in the absence of multiple endocrine neoplasia type 1 (MEN 1) and Carney complex.[55] Prolactinomas associated with FIPA are macroprolactinomas in 36% cases of FIPA with homogeneous clinical expression, i.e. when all affected members of the same family have the same type of pituitary adenoma. This percentage significantly increases to 55.5% in families with heterogeneous FIPA, when different types of pituitary adenomas are expressed in the same family.[53] This finding may be in relation to the presence of a greater number of males in the latter group.[53] *AIP* (aryl hydrocarbon receptor-interacting protein) gene mutations appear in 15% of patients with FIPA and are associated with 10–20% of macroadenomas that usually develop in children, adolescents and young adults.[56–58]

Macroprolactinoma associated to MEN 1

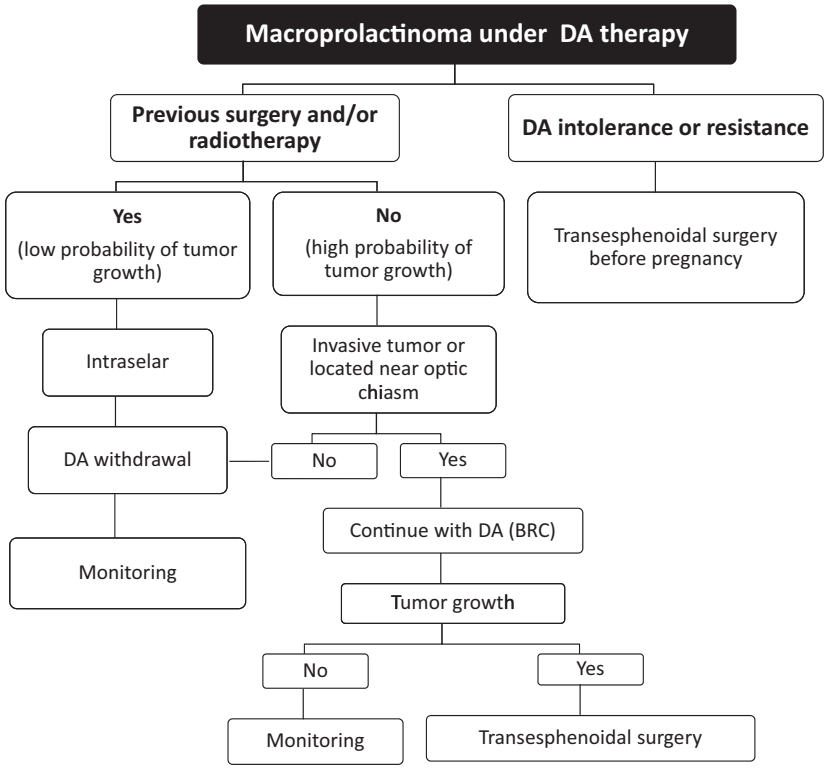
MEN 1 is an autosomal dominant hereditary syndrome characterized by the coexistence of parathyroid, pituitary and gastroenteropancreatic (GEP) tumors associated with mutations in the gene *MEN 1*, a suppressor gene located on chromosome 11q13 that encodes the menin protein.[59,60] Primary hyperparathyroidism is the most common disorder (>90%) associated to MEN 1, followed by GEP tumors (30–75%), while pituitary tumors appear in 10–60% of patients.[59,61] Among them, prolactinomas are most common (~20%). In turn, prolactinomas are usually macroprolactinomas in ~85% of the patients and 30% of the cases being invasive macroprolactinomas.[61] Some studies suggest that macroprolactinomas associated with MEN 1 are larger, more aggressive and with poorer therapeutic response than the sporadic macroprolactinomas not associated with MEN.[60–62]

Macroprolactinoma and pregnancy

Due to the stimulating effect of placental estrogens on the lactotrope cells, macroprolactinomas can grow during pregnancy and therefore be accompanied by local complications (headache and/or visual disturbances). The possibility of growth of macroprolactinoma during pregnancy varies according to whether patients have been or not previously treated with surgery and/or radiotherapy. In the first case, growth is observed in 2.5–4.8% of pregnant women, whereas in the second, the percentage increases to 9–31%.[38,63–65] In women who do not tolerate DA or not achieve an appropriate response with reduction of tumor size with the pharmacological treatment, surgery of the macroprolactinoma prior to pregnancy is recommended.[37] Although the withdrawal of treatment with DA before pregnancy is recommended, it is considered prudent to continue with treatment, preferably with DA (BRC) throughout the pregnancy in women who have not been operated or irradiated previously, especially in invasive tumors or located near the optic chiasm.[37,66] The occurrence of headaches or new alterations in the visual field requires the realization of visual field evaluation or assessment and MRI without paramagnetic contrast (gadolinium).[37] In the case of symptomatic growth of the macroprolactinoma, one can choose changing treatment from BRC to CAB[67,68] and, in the absence of response, consider transesphenoidal surgery in the second trimester of pregnancy[63,66] (Figure 4).

Cystic macroprolactinoma

Although in the majority of patients, macroprolactinomas are solid, sometimes, it may be cystic as consequence of the resolution of a previous intratumoral hemorrhage, necrosis of the tumor or other factors such as radiation therapy, steroid treatment, anticoagulation, trauma and DA treatment.[69,70] Cystic macroprolactinomas may appear in patients of any age. In fact, they have been reported in both children[15,17] and adults.[69,71] It has been suggested that cystic macroprolactinomas do not respond well to medical treatment due to the absence of dopamine receptors in the cystic area of the tumor. Therefore, some authors recommend surgery as the first therapeutic option, especially if there is a visual compromise.[50,72] However, the solid component of the tumor maintains responsiveness to DA, so treatment with these drugs contributes to a reduction of the tumor mass. A small number of patients with cystic macroprolactinomas treated only with DA has been reported so far.[69,71] Results indicate that approximately half of the patients achieve normalization of seurm PRL, radiological cure and tumor size reduction.[69] With these results, medical treatment with DA should be considered as the first-line therapy prior to surgery in cystic macroprolactinomas. Finally, it should be taken into account that the treatment with DA can



Abbreviations: DA, dopamine agonists; BRC, bromocriptine

Figure 4. Therapeutic algorithm for macroprolactinoma before and during pregnancy.

give rise to the development of pituitary apoplexy in cystic macroprolactinomas.[73]

Giant prolactinoma

Giant prolactinoma is defined as a macroprolactinoma with diameter $\geqslant 4$ cm or more than 2 cm of suprasellar extension. It is a rare tumor that occurs mainly in males (~85%), ~25% of them being macroprolactinomas and with an estimated frequency of 0.5–4.4% from all pituitary tumors.[19,74–76]

Symptoms of giant prolactinoma depends not only on the hyperprolactinemia but also on tumor mass effect and are associated to neuro-ophthalmological complications.[77] These patients have an increased risk of pituitary apoplexy,[78] intratumoral hemorrhage,[7] cerebrospinal fluid fistula with rhinoliquorrhea[79,80] and other exceptional complications as epistaxis,[81] proptosis,[82] nasal obstruction,[83,84] recurrent sinusitis,[84] seizures,[85] hydrocephalia[20] and even osteoarticular affection.[86]

Serum PRL levels associated with giant prolactinoma are very high, usually >1000 ng/ml, with levels, occasionally exceeding 40 000 ng/ml.[87,88] Sometimes PRL levels are so high that they can appear in the urine in the form of nephrotic range proteinuria.[89] There is no correlation between tumor size and PRL levels in giant prolactinoma.[74]

The treatment of choice, and therefore of first line, of giant prolactinoma is medical treatment with DA, especially CAB.[17,35,74-76,83,87,88,90–96] Therapy with CAB is associated to a normalization of PRL levels in 68%, a 73% of reduction of tumor size and an improvement of the visual field in 91% of the patients.[75,76,83,88] Surgery should be indicated when the patient is intolerant or tumor resistant to medical treatment with DA and continues to grow causing neuro-ophthalmological involvement or when it produces a rapid loss of vision or paralysis of cranial nerves due to intratumoral hemorrhage or pituitary apoplexy.[37,75,97] Radiotherapy has a limited role in the treatment of giant prolactinoma; on the one hand, due to its questionable efficacy[98] and, on the other hand, the good response to the DA and the complications associated with radiotherapy, especially hypopituitarism.[19] Therefore, radiation therapy would be reserved for patients with tumors resistant to DA that cannot be treated surgically. Although prolactinomas may express the subtypes of receptors for somatostatin (SS) 2, 3 and 5, therapy with SS analogs is generally ineffective; however, recently it has been reported the first case of a male with aggressive giant prolactinoma resistant

to DA that presented an appropriate response to treatment with ^{111}In-DTPA-octreotide.[99]

Finally, it must not be forgotten that the reduction in tumor size induced by DA may be accompanied by serious complications such as fistula of cerebrospinal fluid with rhinoliquorrhea[14,79,100,101] or otoliquorrhea,[102] pituitary apoplexy,[73] intratumoral hemorrhage,[32] cerebral and or optic chiasm herniation into the sella turcica associated with seizures and/or visual alterations[33] and, finally, tension pneumocephalus.[103]

Malignant prolactinoma

Macroprolactinoma may also have a malignant behavior. In this case it is considered as a PRL secreting pituitary carcinoma or malignant prolactinoma. Pituitary carcinoma is defined by the presence of distance metastasis. It is a rare entity with around 165 cases described so far,[104,105] of which about one-third are malignant prolactinomas.[2,106] Clinically it shows no special signs to help distinguish it from the usual macroprolactinoma. Occasionally, the morphological study shows similar images to those found in the macroadenoma.[107] PRL levels are similar to the macroprolactinoma. Diagnosis is suspected when the prolactinoma is refractory to medical therapy or in those cases with high rate of recurrence and the diagnosis is established, when distant metastases are found, usually located at central nervous system.[2,107,108] Although treatment with DA can be effective for treating metastases, tumor regression may not occur to be transient. The standard chemotherapy or radiation therapy has not shown to be effective.[109–112] The use of temozolomide (TMZ), an alkylating agent used in the treatment of glioblastoma multiforme, has been accompanied by good results obtaining long-term partial responses.[111,112]

Conclusion

Macroprolactinoma is a rare tumor with increasing incidence in young people and men, whose biological behavior seems to be more aggressive. Clinically, it manifests in the form of visual disturbances and/or headaches due to the compressive effect of the tumor and symptoms arising from the hyperprolactinemia. PRL levels tend to be generally >250 ng/ml and are correlated with the size of the tumor. Treatment of choice, and therefore, of first line for all macroprolactinomas regardless of size, are DA, mainly CAB, achieving in a high percentage of patients a significant reduction in PRL levels, the restoration of the gonadal function and a significant reduction in tumor size. Surgery should be relegated to those cases of DA resistance, intolerance or lack of adherence to medical treatment, neuro-ophthalmologic defects associated with intratumoral hemorrhage or pituitary apoplexy. Radiation therapy would be reserved to a poor response to surgical treatment and in the case of malignant prolactinomas. TMZ has shown its effectiveness in the case of malignant prolactinoma. Today, the use of DA (BRC) is a therapeutic option in pregnant women bearing macroprolactinomas not previously treated by surgery and/or radiotherapy, especially in invasive macroprolactinomas and in those located near the optic chiasm, due to the potential growth during pregnancy.

Conflict of interest: None declared.

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