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Annales d'Endocrinologie 77 (2016) 641–648

Annales d'Endocrinologie
Annals of Endocrinology

Original article

Long-term outcome of macroprolactinomas

Devenir à long terme de patients porteurs de macroprolactinomes

Lori Képénékian [a], Hélène Cebula [b], Frédéric Castinetti [c], Thomas Graillon [d], Thierry Brue [c], Bernard Goichot [a,e,*]

[a] *Service de médecine interne, nutrition et endocrinologie, hôpital de Hautepierre, University Hospital of Strasbourg, 1, avenue Molière, 67098 Strasbourg cedex, France*
[b] *Service de neurochirurgie, hôpital de Hautepierre, University Hospital of Strasbourg, 1, avenue Molière, 67098 Strasbourg cedex, France*
[c] *CRN2M-UMR7286, service d'endocrinologie et centre de référence des maladies rares d'origine hypophysaire DEFHY, Aix-Marseille University, CNRS, Assistance publique–Hôpitaux de Marseille (AP–HM), hôpital Timone, 264, rue Saint-Pierre, 13385 Marseille cedex 15, France*
[d] *Service de neurochirurgie, hôpital Timone, Assistance publique–Hôpitaux de Marseille (AP–HM), 264, rue Saint-Pierre, 13385 Marseille cedex 15, France*
[e] *Faculty of Medicine, University of Strasbourg, 4, rue Kirschleger, 67000 Strasbourg, France*

Abstract

Objective. – Management of macroprolactinomas has dramatically changed in recent decades, from surgical to medical treatment as first-line therapy, with the development of dopamine agonists (DA). But few data exist on the long-term outcome of these patients. *Patients and methods.* – Retrospective descriptive multicenter study of patients with macroprolactinoma followed for at least 5 years between 1973 and 2008 at the University Hospitals of Strasbourg and Marseille. *Results.* – Forty-eight patients were included with 27 men, hypopituitarism in 33.3% of all patients and mean serum prolactin (PRL) level at diagnosis 2218.2 ± 4154.7 μg/L. Among the patients, 58.3% received medical treatment, 25% had additional surgery and 12.5% surgery and radiotherapy. The mean follow-up duration was 196 ± 100 months. At the end of follow-up, 10 patients (20.8%) were cured (i.e. normal PRL level and normal imaging, no symptoms and withdrawal of DA ≥ 1 year), 33 (68.8%) were controlled (i.e. normal PRL level, normal or abnormal imaging, no symptoms, DA in progress) and 5 (10.4%) were uncontrolled. Uncontrolled patients had significant higher baseline PRL level ($P = 0.0412$) and cabergoline cumulative dose ($P = 0.0065$) compared to the controlled group. There was no increase in frequency of hypopituitarism. Clinically significant valvular heart disease was found in 2 patients but screening was not systematic. *Conclusions.* – Macroprolactinoma is currently most often a chronic disease controlled with DA. However, uncertainty about the adverse effects associated with high cumulative doses and the lack of data on the prognosis at very long-term should incite to revisit current strategies, including the role of surgery combined to medical treatment.
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Keywords: Dopamine agonists; Macroprolactinoma; Hyperprolactinemia; Prolactin; Valvulopathy; Outcome

Résumé

Objectif. – Le traitement des macroprolactinomes a considérablement évolué, de la chirurgie vers un traitement médical par agonistes dopaminergiques (AD) prescrits en premier intention. Mais peu de données existent sur le pronostic à long terme de ces patients. *Patients et méthodes.* – Étude descriptive rétrospective multicentrique de patients porteurs d'un macroprolactinome, suivis pendant au moins 5 ans, entre 1973 et 2008 aux CHU de Strasbourg et de Marseille. *Résultats.* – Quarante-huit patients ont été inclus dont 27 hommes, 33,3 % de patients en insuffisance antéhypophysaire, prolactine (PRL) moyenne initiale 2218,2 ± 4154,7 μg/L. Parmi les patients, 58,3 % ont eu un traitement médical, 25 % une chirurgie complémentaire et 12,5 % chirurgie et radiothérapie. Le suivi moyen était de 196 ± 100 mois. Au terme du suivi, 10 patients (20,8 %) étaient guéris (i.e. PRL/imagerie normales, absence de symptômes et arrêt des AD ≥ 1 an), 33 (68,8 %) étaient contrôlés (i.e. PRL normale, imagerie normale ou non, absence de symptômes, AD en cours) et 5 (10,4 %) n'étaient pas contrôlés. Les patients non contrôlés avaient une PRL initiale ($P = 0,0412$)

* Corresponding author. Service de médecine interne, nutrition et endocrinologie, hôpitaux universitaires de Strasbourg, hôpital de Hautepierre, 1, avenue Molière, 67098 Strasbourg cedex, France.
E-mail address: bernard.goichot@chru-strasbourg.fr (B. Goichot).

http://dx.doi.org/10.1016/j.ando.2016.07.004
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et une dose cumulée de cabergoline ($P = 0{,}0065$) plus élevées que les patients contrôlés. Le taux d'hypopituitarisme n'était pas augmenté. Deux valvulopathies significatives étaient retrouvées mais la recherche n'a pas été systématique. *Discussion.* – Le macroprolactinome doit être considéré comme une maladie chronique contrôlée par les AD. Mais les incertitudes sur les effets indésirables liés à de fortes doses cumulées et le manque de données sur le pronostic à très long terme devraient faire rediscuter des stratégies actuelles, notamment de la place de la chirurgie combinée au traitement médical.
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Mots clés : Agonistes dopaminergiques ; Macroprolactinome ; Hyperprolactinémie ; Prolactine ; Valvulopathie ; Évolution

1. Introduction

Prolactinomas are the most frequently functioning pituitary tumour, accounting for approximately 40% of pituitary tumors [1,2]. Over 90% of prolactinomas are microprolactinomas (< 10 mm in diameter), while the remaining 10% are macroprolactinomas (≥ 10 mm in diameter) [3,4]. These are more frequently reported in men [5,6] with a macro:microprolactinoma ratio of 5:1 [7].

The management of these macroprolactinomas has significantly evolved over the past decades with the development of dopamine agonists (DA). Before the mid-1980s, the first-line treatment was surgery [8]. However, normal prolactin (PRL) levels and complete surgical resection was achieved in up to a third of patients and longer-term cure was reported in only a quarter of patients [1]. Then the onset of DA (quinagolide, pergolide, bromocriptine), that proved efficiency to normalize PRL level, restoration of gonadal function and tumor shrinkage [1,9], however less marked in macroprolactinomas, have dramatically changed the therapeutic strategy. DA became the first-line therapy in macroprolactinomas, while surgery was still preferred in microprolactinomas. Since 1996 and the placing on the market of cabergoline, a new DA better tolerated with longer half-life, medical treatment has become the first-line therapy for both micro- and macroprolactinomas, surgery coming in second-line, in case of resistance, intolerance or poor observance to medical treatment [10,11]. Radiotherapy comes only after failure of medical and/or surgical therapy.

Nevertheless, this therapeutic approach involves prolonged, sometimes lifelong, treatment in young patients, often diagnosed before the age of 40 years [12] and issue after withdrawal of DA being uncertain [13,14]. Moreover, several studies have shown an increased risk of valvulopathy in patients treated with DA for Parkinson's disease, including cabergoline and pergolide [15,16], with a dose–response relationship, confirmed by other data in the literature [17,18]. Although the doses needed to treat patients with macroprolactinomas are generally lower, the absence of valvular risk has not been clearly demonstrated [19], questioning the current therapeutic strategy, which includes long-term medical treatment.

The aim of our study was to evaluate the long-term outcome of patients with macroprolactinoma according to the treatments received.

2. Subjects and methods

We conducted a retrospective descriptive multicenter study in patients with macroprolactinomas, defined as the combination of hyperprolactinemia ≥ 100 μg/L and a pituitary mass ≥ 10 mm, having been followed up for at least 5 years between 1973 and 2008 in the department of Internal Medicine, Endocrinology and Nutrition of the University Hospital of Strasbourg and the department of Endocrinology, Diabetes and Metabolic Diseases of University Hospital of Marseille.

Clinical files were selected from the data of the Department of Medical Information (DMI). The inclusion criteria were hospitalisation in the department with main diagnosis "benign pituitary tumor", "hyperprolactinemia", "malignant pituitary tumor" or "pituitary tumor of uncertain or unknown prognosis", which represented 1472 cases. From this selection, only patients with macroprolactinoma and a follow-up duration longer than 5 years were included.

A review of the clinical notes was undertaken. We recorded the date of diagnosis, symptoms at diagnosis, baseline PRL level and imaging (CT or MRI), whether or not a cosecretion, visual field defect, hypopituitarism or hereditary syndrome associated, all treatments received until the last clinic visit, type/dose and duration of DA treatment received throughout the follow-up (quinagolide, bromocriptine, cabergoline), response to treatment with normalization of PRL level and imaging and their delay. At the last clinic visit, we collected symptoms, last PRL level and imaging, presence or absence of hypopituitarism and valvulopathy at echocardiography (when available).

The duration of follow-up was calculated as the interval between the date of diagnosis and the last clinic visit.

Concerning valvular heart disease evaluation, the American Society of Echocardiography (ASEC) and the European Association of Echocardiography (EAE) have issued recommendations for the assessment of valvular insufficiencies with a scale from 0 to 4 (grade 0: no regurgitation, 1: "trace", 2: "mild", 3: "moderate", 4: "severe") [20]. Lesions are clinically significant from grade 3 for mitral, tricuspid and pulmonary valves and from grade 2 for aortic valve.

PRL levels are indicative, in the absence of standardization of assays. Indeed, given the long period covered and the multicenter nature of the study, many different assays were used. PRL levels before treatment was administered were available in 39/48 patients.

Patients were divided into three groups according to their status at the last clinic visit:

- a "cured" group defined by the absence of clinical symptoms, normal PRL level, normal imaging and withdrawal of DA treatment ≥ 1 year;

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