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Review

Update on prolactinomas. Part 2: Treatment and management strategies

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ABSTRACT

The authors present an update on the various treatment modalities and discuss management strategies for prolactinomas. Prolactinomas are the most common type of functional pituitary tumor. Effective hyperprolactinemia treatment is of great importance, due to its potential deleterious effects including infertility, gonadal dysfunction and osteoporosis. Dopamine agonist therapy is the first line of treatment for prolactinomas because of its effectiveness in normalizing serum prolactin levels and shrinking tumor size. Though withdrawal of dopamine agonist treatment is safe and may be implemented following certain recommendations, recurrence of disease after cessation of the drug occurs in a substantial proportion of patients. Concerns regarding the safety of dopamine agonists have been raised, but its safety profile remains high, allowing its use during pregnancy. Surgery is typically indicated for patients who are resistant to medical therapy or intolerant of its adverse side effects, or are experiencing progressive tumor growth. Surgical resection can also be considered as a primary treatment for those with smaller focal tumors where a biochemical cure can be expected as an alternative to lifelong dopamine agonist treatment. Stereotactic radiosurgery also serves as an option for those refractory to medical and surgical therapy.

1. Introduction

Prolactinomas are the most common hormone-secreting pituitary tumors, accounting for approximately 40% of all pituitary tumors and 50–60% of all functional pituitary tumors [1–3]. Patients typically present with clinical features of hyperprolactinemia, including gonadal dysfunction, amenorrhea and galactorrhea. Patients with large tumors may also experience headaches and visual field disturbances [4].

The primary goals of treatment for hyperprolactinemia are to alleviate the clinical consequences of excessive hormone secretion, restore gonadal and sexual function by normalizing serum prolactin levels, preserve residual pituitary function, and prevent disease recurrence or progression [2,5]. While pharmacological therapy with dopamine agonists remain the standard of care [6–8], surgical removal in various instances may be necessary in the management of some prolactinomas [9,10]. Our understanding of the pathogenesis and clinical manifestation of prolactinomas continues to evolve. In addition, significant advances in the last few decades, including more sensitive diagnostic hormone assays, neuroimaging methods, pharmacological therapies, and more refined endoscopic surgical techniques, have contributed to the contemporary management of prolactinomas. In this paper, we discuss the current management strategies for patients with prolactinomas, including the role of medical treatment, its challenges during pregnancy, withdrawals and resistance, indications for surgical treatment and the role it plays in microprolactinomas and macroprolactinomas, and finally, radiation therapy.

2. Medical treatment

The primary goals of treatment for hyperprolactinemia are to alleviate the clinical consequences of excessive hormone secretion, restore gonadal and sexual function by normalizing serum prolactin levels, preserve residual pituitary function, and prevent disease recurrence or progression [2,5]. The goals of treatment for hyperprolactinemia due to prolactinomas are to: normalize prolactin levels and ameliorate its clinical consequences, allowing restoration of fertility and sexual function; reduce tumor mass effect to potentially relieve visual defects and cranial nerve palsies; preserve residual pituitary function; prevent disease recurrence or progression [1,2,8,11]. In patients with macroadenomas, it is also important to control and reduce the tumor size [5]. Those with

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asymptomatic microprolactinomas may not require treatment, as microprolactinomas rarely grow to a significant extent [12,13]. Nonetheless, it is advised to closely monitor untreated microprolactinomas for potential enlargements and development of symptomatic hyperprolactinemia.

Hypothalamic control of prolactin production and release is mediated by the tonic inhibition of dopamine [14]. Dopamine agonists act on dopamine D2-type receptors on pituitary lactotroph cells, leading to a decrease in the synthesis and release of prolactin [4]. Dopamine agonist therapy has also shown marked reductions in tumor size via mechanisms that are not yet fully understood [4].

Pharmacological therapy with dopamine agonists is the first line of treatment for prolactinomas due to its effectiveness in normalizing prolactin levels, reducing tumor volume, and restoring gonadal function (Fig. 1) [2,15]. For most microprolactinomas, dopamine agonists restore gonadal function in 80–90% of patients [16,17]. Normalization of prolactin levels may be achieved in up to 85% of patients with previously untreated macroprolactinoma, with tumor shrinkage of at least 25% seen in approximately 80% [16]. While on medical treatment, the patient's serum prolactin levels should be monitored yearly [2]. Two dopamine agonists, bromocriptine and cabergoline, are approved for use in the USA.

The safety of ergot-derived dopamine agonists, particularly cabergoline and pergolide, has been questioned due to recent studies demonstrating an association between the use of these medications in Parkinson's disease and cardiac valvulopathy [18]. These adverse effects seen in Parkinson's patients are reflective of the high mean cumulative dose of the dopamine agonists. The dosage administered for the treatment of hyperprolactinemia is much lower than the dose used for the treatment of Parkinson's disease [19]. To date, there is no evidence of a significant association between cabergoline treatment for hyperprolactinemia and cardiac valvulopathy [20–23]. However, larger longitudinal studies with longer follow-up durations, especially of those on higher doses of cabergoline, are suggested to confirm these findings [23]. While dopamine agonists have been deemed a safe treatment for hyperprolactinemia, patients who are on prolonged cabergoline treatment should undergo echocardiographic surveillance to monitor for possible changes [22].

2.1. Bromocriptine

Bromocriptine is an ergot derivative with potent dopamine receptor agonist activity. It is a D2 selective dopamine agonist and a D1 antagonist, and it has been used for over three decades [12]. Its short half-life usually requires it to be administered 2–3 times daily. The dosage typically starts at 0.62–1.25 mg/day and is increased by 1.25 mg every week, up to 30 mg/day. While bromocriptine has satisfactorily treated hyperprolactinemia for many years, it has many side effects. These include gastrointestinal (nausea, vomiting, constipation, reflux, dyspepsia), neurological (headache, dizziness, dyskinesia, confusion), cardiovascular (postural hypotension, syncope), and other side effects such as muscle cramps, psychosis and dry mouth. These are quite common and increase with dosage and/or as drug compliance decreases [12].

2.2. Cabergoline and other dopamine agonists

Cabergoline is an ergoline D2 agonist that has a long half-life, enabling oral administration only once or twice weekly [12]. The dosage typically starts at 0.25–0.5 mg/week and is increased weekly until normal prolactin levels are achieved [12]. Cabergoline is the primary pharmacological treatment for aggressive macroprolactinomas [15,16,24]. It is also efficacious in managing hyperprolactinemia and tumor shrinkage in patients who are either resistant or intolerant to bromocriptine [25]. Figure 1

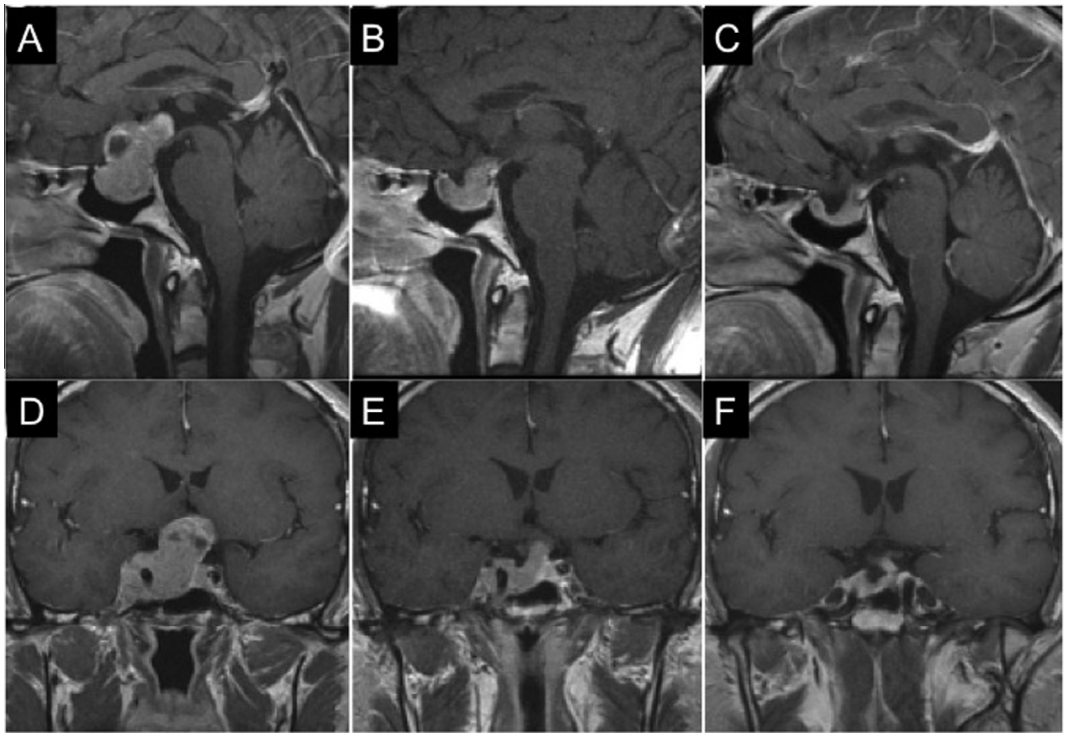

Fig. 1. Initial post-gadolinium T1-weighted MRI (A: sagittal; D: coronal) of a 41-year-old man who presented with headaches and blurred vision secondary to a macroprolactinoma. His serum prolactin level was 3711.0 ng/mL. Bromocriptine therapy was initiated and a follow-up MRI (B: sagittal; E: coronal) 3 months later showed significant tumor shrinkage, and he had a serum prolactin level of 196.7 ng/mL. One year later, the patient developed resistance to bromocriptine with recurrent tumor growth. Bromocriptine was switched to cabergoline and a follow-up MRI (C: sagittal; F: coronal) 4 months later showed further shrinkage of the tumor volume. His serum prolactin level was 56.7 ng/mL.