

Spontaneous reduction of prolactinoma post cabergoline withdrawal

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ABSTRACT

Prolactinomas are common pituitary tumors usually highly responsive to dopamine agonists. Around 70-90% of the prolactinomas exhibit decrease in tumor size, though variably with these agents. Uncommonly, there may be little or no shrinkage in pituitary tumor. In the absence of medical therapy, pituitary apoplexy may also result in tumor shrinkage, albeit rarely. We report here a case showing only modest reduction in prolactinoma with cabergoline given for a period of one and a half years. Surprisingly, this tumor showed a 40% reduction in the tumor size 3 months after cabergoline withdrawal in the absence of clinical or radiological evidence of apoplexy.

Key words: Cabergoline withdrawal, prolactinoma, spontaneous involution

INTRODUCTION

Tumors arising from lactotrope cells account for about half of all functioning pituitary tumors. Oral dopamine agonists (cabergoline or bromocriptine) are the mainstay of therapy for patients with prolactinomas. Dopamine agonists suppress prolactin secretion and synthesis as well as lactotrope cell proliferation. About 10-30% of patients are resistant to dopamine agonists, these adenomas may exhibit decreased D2 dopamine receptor numbers or a postreceptor defect.^[1,2] Pharmacologic resistance to DA agonists has been variously defined and refers to failure to respond to such agents in terms of either normalization of PRL levels, or reduction of prolactin levels by 50% or a reduction in tumor size by at least 50%.^[2,3] Resistance to bromocriptine therapy is common with almost 25-30% of patients showing failure to normalize PRL levels.^[1,4] On the other hand, resistance to cabergoline therapy is described rarely in only around 4-9% of patients.^[2,5,6]

Shrinkage of tumor usually occurs while on dopamine agonist therapy. Histopathological specimens reveal involution of the endoplasmic reticulum and golgi apparatus with shrinkage of individual cells in most cases.^[7,8] Rarely, involution of tumor may also occur post pituitary apoplexy in treatment naïve patients. We report here a case who showed biochemical response; however, there was no change in tumor size over 2 years with cabergoline treatment. Surprisingly, there was a 40% reduction in tumor size in the absence of clinical or radiological evidence of apoplexy after 3 months of stopping cabergoline.

CASE REPORT

A 48-year-old male presented to the endocrinology department of this hospital with complaints of episodic headache for the past 10 years, with increasing severity for 2 years. There were no complaints suggestive of visual field defects. The patient also complained of decreased libido and erectile dysfunction. His shaving frequency had decreased to once per week. He had been a diabetic for four years and had been well controlled on metformin. Examination including genitalia and virilization was essentially normal, galactorrhea was absent. MRI sella revealed a large pituitary lesion (13×10 mm) in the right half of pituitary gland [Figure 1]. Prolactin levels were 557.67 ng/ml (3-20ng/ml). LH, FSH and testosterone levels were 0.81, 0.38 and

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1.56 ng/ml respectively. Thyroid profile and serum cortisol levels were normal. A diagnosis of prolactinoma was made and the patient was started on cabergoline 0.5 mg thrice a week. The prolactin levels gradually came down to normal over a period of 3-4 months (51, 19, and 14 ng/ml over consecutive month). Improvement in sexual functions was also reported by the patient. Prolactin levels remained normal with cabergoline. MRI done 4 months later showed around 15% reduction in tumor size (11×10 mm) [Figure 2]. However, MRI done one year later showed no significant change in mass (10×9 mm) [Figure 3]. He also complained of daily headaches requiring analgesics. Cabergoline was stopped and the patient was referred to neurosurgery for further intervention. After 3 months, a repeat MRI was done, which surprisingly showed a significant (40%) reduction in size of pituitary tumor (6×5 mm) [Figure 4]. Patient reported improvement in headache with frequency now reduced to once a week. There was modest elevation of prolactin levels from 11.7 to 34.2 ng/ml. Decrease in libido was managed with testosterone injections.

DISCUSSION

Dopamine agonists inhibit PRL secretion by activation of lactotroph dopamine D2 receptors. Activation of the D2 receptor results in the inhibition of PRL synthesis and secretion through a number of pathways mediated by several G proteins. Gai2 mediates D2-induced adenylyclase inhibition which is probably the major pathway involved in decreasing PRL gene transcription,^[9,10] as well as the inhibition of phospholipase C,^[11] which is necessary for activation of phosphoinositide pathways.^[12] Gao also couples the D2 receptor to constitutive and hormone stimulated levels of activated mitogen activated protein kinase (MAPK) and extracellular signal regulated kinases (ERK1 and ERK2), thereby inhibiting cell proliferation.^[13,14] A number of mechanisms have been proposed to explain resistance to dopamine agonists in patients with prolactinoma. These include decreased absorption of medication, decreased number of D2 receptors, and

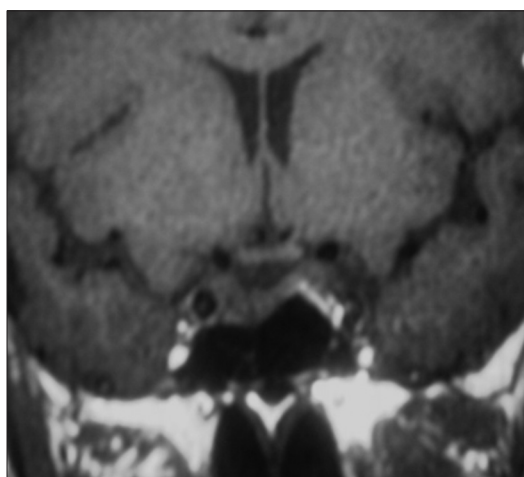


Figure 1: Coronal T1 WI of sella reveals a hypointense mass lesion involving the right half of pituitary gland of size 13 × 10 mm

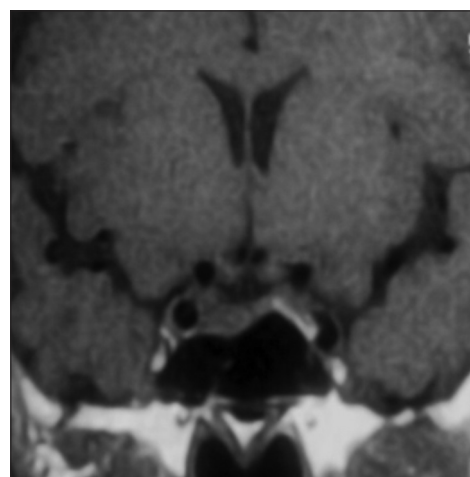


Figure 2: Follow-up MRI scan at 4 months reveals mild (15%) reduction in tumor size

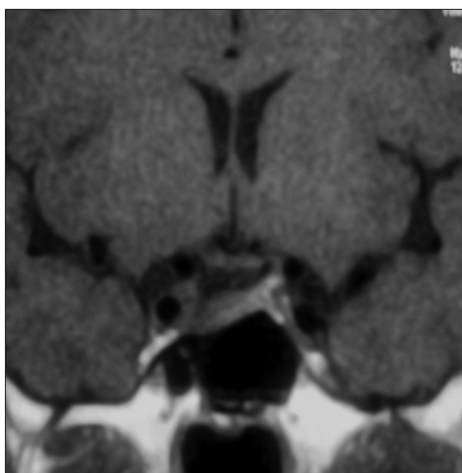


Figure 3: MRI sella at 1 year interval shows no significant change

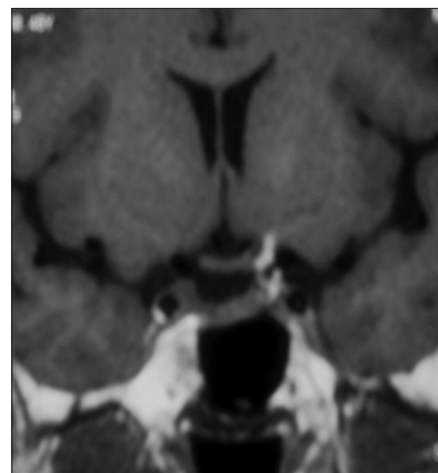


Figure 4: MRI scan (post cabergoline withdrawal) shows a significant (40%) reduction in tumor size

decreased affinity of the D2 receptors for the dopamine agonists and altered intracellular signal transduction in the resistant tumor.

Involution of prolactinomas usually occurs while on dopamine agonist therapy. The histopathological findings include shrunken island-like cell nests, acellular spaces consisting of hyaline substance and fibrosis, and degenerative necrotic tumor cells.^[15] The regression of tumors with dopamine agonists may either occur concurrently or may be delayed long after hormonal reduction. The delayed effect of dopamine agonists after stopping therapy was systematically analyzed in a meta-analysis of 19 studies involving 743 patients by Dekkers *et al.*^[16] Normoprolactinemia was variously reported between 0 and 74% in different studies after at least 6 months of dopamine agonist withdrawal. However, there was no evaluation of the tumor size in the post drug withdrawal period in this study. Involution of prolactinomas may also occur post pituitary apoplexy.^[17] Pituitary hemorrhage is commonly associated with the use of dopamine agonists, but may also occur in the absence of any treatment. Although coagulation disorders, sepsis or systemic illness are known to precipitate pituitary apoplexy, the underlying mechanisms are poorly understood.

Our present case showed prompt reduction in the prolactin levels and some initial decrease in tumor size with cabergoline therapy. However, there was no subsequent decrease in tumor size after one year of therapy. Surprisingly this patient showed a 40% reduction in tumor size and only modest increase in prolactin levels after 3 months of withdrawal of therapy. There were no apparent clinical signs or radiological evidence to suggest pituitary apoplexy. Rainov *et al.* described spontaneous reduction of macroprolactinoma in a male patient over a period of 6 months without therapy.^[18] It is possible that a silent pituitary apoplexy or a delayed atrophic effect of dopamine agonists may have caused tumor reduction in the present case. However, on cabergoline therapy there was only a marginal reduction in tumor size.

In conclusion, this is a rare case of prolactinoma where tumor reduction is observed after withdrawal of the dopamine agonists.

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