

## Schizophrenia and Macroprolactinoma: Is There a Deep Link?

### Abstract

Prolactinomas are the most common type of functional pituitary tumors. Dopamine agonists is the most important drugs used in prolactinoma, have antagonistic effect with antipsychotic drugs used in schizophrenia. Conversely, dopamine antagonist drugs increase prolactin in patients with simultaneous schizophrenia. In the present case, we report a 29-year-old single male with schizophrenia who treated for 8 years with risperidone and presented with macroprolactinoma. Iatrogenic hyperprolactinemia is a well-known side effect of dopamine antagonist drugs for treatment in a patient with schizophrenia. On the other hand, it appears these drugs have the other side effects, such as drug-induced prolactinoma or boost growth.

**Keywords:** Antipsychotic agents, case reports, dopamine antagonists, prolactinoma, schizophrenia

### Introduction

Pituitary tumors contain about 10%–15% of all intracranial tumors.<sup>[1]</sup> Prolactinomas are the most common type of functional pituitary tumors.<sup>[2]</sup> Macroprolactinomas are tumors larger than 10 mm managed with dopamine agonists (DAs), surgery and radiotherapy. DAs, such as cabergoline, usually used as first-line therapy for uncomplicated patients with macroprolactinomas. Some antipsychotic drugs block dopamine via dopamine D2 receptors (D2Rs), which can cause an increase in blood prolactin levels.<sup>[3]</sup>

The treatment of a patient with macroprolactinoma and a concomitant psychotic disorder demonstrates a special challenge: psychotic symptoms mostly treat with the D2R antagonists, and the majority of antipsychotic agents can cause notable increases in prolactin (PRL) levels as side effects, which is particularly undesirable in patients with macroprolactinoma. Simultaneously, treatment with DAs may worsen psychotic symptoms.<sup>[4]</sup>

Due to the rarity of this condition, we aim to describe a concurrency of macroprolactinoma in a patient with long-term use of antipsychotic drugs for schizophrenia treatment.

### Case Report

A 29-year-old male was referred to the Endocrinology Department of Al-Zahra Hospital in Isfahan on September 2018. The patient presented with complaints of headache, visual field loss, and eye pain. He was referred for treatment since he was 21 years, due to obsessive-compulsive thoughts, sleep disorders, and visual and auditory hallucinations. Brain imaging was normal and treatment with risperidone and perphenazine was started.

At the age of 28, the patient experienced a visual field loss in both eyes. Laboratory examinations showed serum PRL levels above 1500 ng/ml (normal range in male: 2–18 ng/ml). Thyroid axis (thyroid-stimulating hormone and T4 levels) and gonadal axis (luteinizing hormone, follicle-stimulating hormone and testosterone levels) were subnormal. Adrenal axis was intact. Magnetic resonance imaging (MRI) showed a pituitary macroadenoma causing compression of the optic chiasm.

According to the tests, the diagnosis of macroprolactinoma was confirmed, and then cabergoline and levothyroxine were prescribed. Based on psychiatric consultation, risperidone and perphenazine

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were stopped, and the patient was treated with aripiprazole and clonazepam. After 3 days, the blurred vision was improved, however, the patient suffered from restlessness, nightmares, frustration, and fear.

The patient was scheduled for trans-sphenoidal surgery. Serum PRL levels reached 52 ng/ml after tumor removal. After surgery, quetiapine, cabergoline and levothyroxine were prescribed.

## Discussion

Schizophrenia is a common psychotic disorder, and its symptoms include hallucinations, delusions, disorganized thinking and grossly disorganized motor behavior.<sup>[5]</sup> The dopamine antagonist drugs are defined as one of the pharmacological treatments for schizophrenia.

Hyperprolactinemia is a recognized side effect of dopamine antagonist drug.<sup>[6]</sup> In this case, we suggest a long duration of treatment with antipsychotics like risperidone increases the chance of developing prolactinoma and its growth.

Dopamine has been shown to induce antimitotic activity on lactotrophic cells by affecting D2Rs. As lactotrophic cells are regulated by dopaminergic tone, loss or reduction of dopaminergic effect is a possible etiologic factor in the development of lactotroph adenomas.<sup>[7]</sup> Asa *et al.*, in a study on D2R-deficient mice, report that both female and male D2R-deficient mice after 17–20 months of age develop pituitary lactotroph adenomas.<sup>[8]</sup>

In the literature review, we found some patients with macroprolactinoma after prolong treatment with D2R antagonist [Table 1].

Akkaya *et al.* followed up three new cases of schizophrenia treated with amisulpride for 6 months to prove the metabolic effects of amisulpride. During follow-up, the PRL level was measured at first, the end of the second

week, and then every month. Cranial MRI taken at the start of treatment showed no abnormality. After 6 months of treatment, MRI of sella was taken to search for the etiology of hyperprolactinemia. In all of patients that treated with amisulpride, MRI of sella showed pituitary microadenomas.<sup>[9]</sup>

## Conclusion

Screening program for hyperprolactinemia may be needed prior to initiating antipsychotic drugs and at regular intervals thereafter for patients using these drugs for a long period of time.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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**Table 1: Reported schizophrenia case presented with prolactinoma**

Therapy	Level of PRL (ng/ml)	Size of prolactinoma	duration of treatment (year)	Psychiatric diagnosis	Age (year)	Sex	study (year)
Chlorpromazine and thioridazine	7981	Large invasive chromophobe adenoma	10	Schizophrenia	40	Male	Richard <i>et al.</i> (1984)
Thioridazine 600 mg/day, diphenylhydantoin 400mg/day	7295	Large prolactin-secreting chromophobe adenoma	15	Schizophrenia	42	Male	Judith <i>et al.</i> (1985)
Olanzapine, ziprasidone	High as 171	Pituitary macroadenoma	4	Schizophrenia	23	Female	Bradley <i>et al.</i> (2007)
Haloperidol 5 mg/day, biperiden 2 mg/day	3616	Macroprolactinoma (25 mm × 20 mm × 12 mm)	10	Schizophrenia	39	Male	Andrade <i>et al.</i> (2010)
Olanzapine 10 mg/day	1986	1.6 cm pituitary macroadenoma (macroprolactinoma)	7	Schizophrenia	25	Male	Shirin <i>et al.</i> (2010)
olanzapine	13,588	Pituitary macroadenoma (28 × mm 24 × mm × 16 mm)	-	Schizophrenia	29	Female	Kah <i>et al.</i> (2010)

PRL: Prolactin

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