CLINICAL VIGNETTE

A Case of Hyperprolactinemia and Pituitary Microadenoma in a Schizophrenic Patient on Antipsychotic Therapy

Eva C. Pessegueiro, M.D., and Antonio M. Pessegueiro, M.D.

Introduction

The association of hyperprolactinemia and pituitary tumors with antipsychotic medications has been described in the literature, particularly with strong dopamine D2-receptor antagonists such as risperidone and haloperidol.[1] Hyperprolactinemia and pituitary tumor in schizophrenic patients may complicate treatment with antipsychotic medications. We highlight the presentation, evaluation, and management of a patient who developed symptomatic hyperprolactinemia and a pituitary microadenoma while on antipsychotic medication.

Case Presentation

A 21-year-old, non-pregnant female with a 3-year history of schizophrenia presented in partial remission to a follow-up appointment with her outpatient psychiatrist. The patient's schizophrenia previously manifested as persecutory auditory hallucinations, religious and paranoid delusions, disorganized speech, and poor level of functioning in interpersonal relations, occupation, and self-care. The patient was highly guarded and paranoid on examination; therefore, most of the history was obtained from the patient's father who accompanied her to this appointment. He reported that the patient had a history of becoming disorganized when psychotic. The patient's father corroborated that she had been taking risperidone (up to 6 mg orally daily) for the past two years. During her last inpatient psychiatric hospitalization three months ago, her antipsychotic therapy had been cross-titrated to haloperidol due to risperidone losing its effectiveness. At this appointment, she was on a regimen that included high doses of haloperidol (20 mg orally twice daily) and benztropine (2 mg orally twice daily). The patient's father stated that this was the best treatment regimen they have had thus far, despite only achieving partial response. He reported the patient to be less delusional and responding less to internal stimuli.

On review of systems, the patient reported several months of galactorrhea without gynecomastia or amenorrhea. She also complained of occasional headaches, not associated with visual changes. These symptoms preceded the recent cross-titration from haloperidol three months ago. Neither the patient nor caregivers had previously mentioned these symptoms to mental health care providers as they were not aware they could be associated with her current medications. Mental status examination revealed an overweight, young Hispanic female who appeared her stated age. She was wearing a casual dress with good grooming and hygiene. She was highly guarded and suspicious of the interviewer with fair eye contact. No psychomotor abnormalities were noted. Mild oral-buccal movements were noted. Her reported mood was "fine." Her affect was blunted, irritable, highly guarded, and oddly related. Her thought process was linear but limited to short answers. Thought content included auditory hallucinations and paranoia. She was future-oriented and not suicidal or homicidal. She was alert and oriented to person, place, time, and situation. Her insight and judgment were severely impaired.

Initial diagnostic evaluation included a comprehensive metabolic panel, complete blood count, thyroid function tests, prolactin, and serum pregnancy test. All laboratory studies were within normal range with exception of an elevated prolactin level of 46.3 ng/mL (reference for non-pregnant female 3-30 ng/mL). Serum pregnancy test was negative. MRI of the brain revealed a 2-mm hypointense region in the pituitary gland, most likely representing a microadenoma.

Initial management included reducing the dose of haloperidol by half over a month, without resolution of galactorrhea. Her auditory hallucinations later returned, and the patient began to destabilize requiring inpatient psychiatric hospitalization. She was changed to aripiprazole and titrated up to 20 mg orally once daily. Endocrinology was consulted, and the patient was started on cabergoline 0.5 mg orally once weekly for a total of three weeks. Her prolactin level 8 weeks later was normal at 12.3 ng/mL, and her galactorrhea had resolved. She developed a dystonic reaction during titration of the aripiprazole, but this improved with benztropine. She was also given low-dose clonazepam for mild akathisia. She eventually returned home with her parents. Fifteen months after discharge, she continues to maintain her baseline stability and has not returned to a psychiatric hospital.

Discussion

The two most common antipsychotic medications associated with pituitary tumors are risperidone and haloperidol due to their strong antagonism of dopamine D2-receptors.[1,2] Our patient had been on both of these medications for an extensive period of time. Long-term treatment with these antipsychotic medications has been shown to promote pituitary tumor growth in animal models.[1-4] Prolonged antagonism of dopamine

receptors leads to hyperprolactinemia, proliferation of pituitary lactotrophs, and microadenoma formation.[3,4]

There is no clear consensus regarding the monitoring of prolactin levels in patients on antipsychotic therapy. Some experts recommend obtaining a baseline prolactin level prior to initiating antipsychotic therapy to help guide a clinician later in deciphering whether a subsequent elevated level is due to medication effect or some other cause.[2] This patient did not have a baseline prolactin measurement. However, given the normalization of her prolactin levels following cross-titration to a prolactin-sparing antipsychotic medication, adverse effects from the previous dopamine antagonizing antipsychotic medications were the most likely etiology for her hyperprolactinemia.

Following initiation of treatment with dopamine antagonizing antipsychotic medications, some suggest that prolactin levels should be monitored during treatment, even in the absence of clinical symptoms since some of the effects of hyperprolactinemia – such as osteoporosis and infertility – may be silent.[5] While some propose testing prolactin levels once at three months following initiation of an antipsychotic medication and thereafter only as side effects appear,[2] others propose annual testing.[6] Females of reproductive age are at highest risk for hyperprolactinemia and pituitary tumor formation.[1,2] This supports more regular screening of women of reproductive age, especially those who are being treated with strong dopamine D2-receptor antagonists such as risperidone and haloperidol.

Clinicians should be mindful that some symptoms of hyperprolactinemia (e.g., galactorrhea, male gynecomastia, amenorrhea, sexual dysfunction, etc.) may be difficult for some patients to discuss openly. It is therefore critical to review these and other potential side effects of antipsychotic therapy with patients regularly. Symptoms of hyperprolactinemia should prompt prolactin testing. Once an elevated prolactin level has been established, evaluation should be performed to rule out other causes of hyperprolactinemia (e.g., pregnancy, breastfeeding, physical or psychological stress, lactotroph adenomas, damage to or interference of dopaminergic neurons in the hypothalamus and pituitary stalk, other drugs, estrogen, hypothyroidism, chronic renal failure [via decreased prolactin clearance], etc.). Imaging, preferably MRI with thin sections through the sellar space and pituitary gland, should be performed if a patient develops any symptoms of a sellar space-occupying lesion (e.g., headache, diplopia, signs, or symptoms related to under- or over-production of pituitary hormones, etc.).[5,7] If a patient is asymptomatic or has mild symptoms with a prolactin level four times greater than the upper limit of normal, then imaging is recommended to rule out a pituitary tumor.[5,7]

The risks and benefits of ongoing treatment should be weighed carefully once hyperprolactinemia related to antipsychotic therapy is suspected. For patients with symptomatic hyperprolactinemia, clinicians may consider either: (a) decreasing the current dose of antipsychotic medication (since hyperprolactinemia is often dose-dependent); or (b) changing to a prolactin-sparing antipsychotic medication such as quetiapine, olanzapine, clozapine, or aripiprazole.[2,5] Lowering the antipsychotic dose for the patient in this case was attempted; however, her symptoms relapsed, and she became psychotic, aggressive, and gravely disabled requiring inpatient psychiatric hospitalization. As the medication was weaned down, she became paranoid and refused to take medications. The patient was therefore transitioned to aripiprazole, a prolactin-sparing antipsychotic.

Other suggested treatment approaches for hyperprolactinemia include adding a dopamine receptor agonist (e.g., amantadine, bromocriptine, or cabergoline); however, this option should be considered if a pituitary tumor is involved.[2,5] Oral contraceptives in women may also help minimize bone mineral density loss and risk for osteopenia and osteoporosis.[2,5]

Conclusion

This young female of reproductive age was psychotic and unable to report symptoms of hyperprolactinemia because of her paranoia and was undergoing aggressive antipsychotic therapy with strong dopamine D2-receptor antagonists. This stratifies her as high-risk for developing hyperprolactinemia with subsequent development of a pituitary tumor. Hyperprolactinemia can be asymptomatic. In our patient, we suspect that she had asymptomatic hyperprolactinemia for quite some time until the levels increased to cause galactorrhea. She did not have a baseline prolactin level to compare, but we assume the elevated level was caused by long-term treatment with risperidone followed by haloperidol. Once those medications were discontinued, the levels of prolactin returned to normal range and her symptoms of galactorrhea resolved.

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