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Case Report

Managing Typical and Atypical Antipsychotic-induced Hyperprolactinemia and Psychosis in a reproductive age female patient: A Case Report

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Abstract

Background: Medications are the most common cause of non-tumoral hyperprolactinemia, and antipsychotics are the primary psychotropics that cause hyperprolactinemia [1]. This occurs more frequently with high-potency, typical antipsychotics (40%-90%) and several atypical antipsychotics with a high potential for hyperprolactinemia, such as risperidone and paliperidone palmitate. However, the incidence of hyperprolactinemia in other atypical antipsychotics (Clozapine, Aripiprazole, Olanzapine) is less reported [2,3]. Risperidone has the highest prevalence (70%-100%) of hyperprolactinemia, whereas prolactin-sparing agent aripiprazole has a lower prevalence (3.1%-9%) [4]. Low-potency atypical antipsychotics are logical alternatives for patients with antipsychotic-induced hyperprolactinemia [2].

Objective: We aim to present a case of a. risperidone-induced hyperprolactinemia managed with Abilify and Clozapine; b. to explore the association of hyperprolactinemia in Typical and Atypical antipsychotics; c. to understand the pathophysiology of hyperprolactinemia; d. to learn the current treatment strategies for managing Antipsychotic-induced hyperprolactinemia.

Case Presentation: This is a case of a 25 years old female with a history of schizoaffective disorder, bipolar type, and treated with risperidone. The patient developed hyperprolactinemia and irregular menstruation. The patient was switched to Fluphenazine, but symptoms of hyperprolactinemia persist. The patient was switched to Aripiprazole. However, hyperprolactinemia was improved, but the psychiatric symptoms continued. The patient was treated with clozapine and aripiprazole with good response psychiatrically with managing the side effects of hyperprolactinemia and irregular menstruation.

Discussion: Hyperprolactinemia, both silent and symptomatic, has negative consequences. Amenorrhea occurs in about 30% of pre-menopausal women due to hyperprolactinemia when treated with risperidone. Hyperprolactinemia also increases the risk of sexual dysfunction, infertility, galactorrhea, decreased bone mineral density, and fracture. When hyperprolactinemia is symptomatic, lowering the dose or switching to a prolactin-sparing antipsychotic (olanzapine, quetiapine, aripiprazole, and clozapine) is recommended [2,5].

Conclusion: Hyperprolactinemia should be evaluated, especially when signs and symptoms are present in patients receiving antipsychotic treatment. Hyperprolactinemia can be reduced using antipsychotics like Clozapine and Aripiprazole.

Introduction

Antipsychotics are the mainstay treatment for psychiatric disorders, including schizophrenia, schizoaffective disorder, and bipolar disorder, requiring long-term and even life-long treatment [6]. Endocrine and adverse metabolic effects are among the most concerning adverse effects while patients are on antipsychotic medications [7]. Among endocrine adverse effects, hyperprolactinemia is a common adverse effect estimated to occur in up to 70% of patients with schizophrenia [3,6].

Typical antipsychotics (e.g., chlorpromazine, perphenazine, and haloperidol) and atypical antipsychotics (e.g., risperidone, paliperidone, and amisulpride) can increase prolactin levels. However, the incidence of hyperprolactinemia is less reported in other atypical antipsychotic medications such as clozapine, aripiprazole, and quetiapine [3]. The propensity to cause hyperprolactinemia differs markedly between antipsychotics

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due to differential dopamine D2 receptor-binding affinity and the ability to cross the blood-brain barrier [8].

Hyperprolactinemia can cause sexual dysfunction, infertility, galactorrhea, decreased bone mineral density, osteoporosis, and fracture in both sexes. Men may develop gynecomastia, and women may develop hirsutism, acne, and menstrual abnormalities such as amenorrhea and oligomenorrhea. These symptoms are not only embarrassing or bothersome but have serious long-term consequences [2]. Clinicians and caregivers need to be aware of potential endocrine adverse effects of antipsychotic medication besides the metabolic side effects [7].

Case Presentation

This patient is 25 years old female with a history of schizoaffective disorder, Bipolar type, who came to the behavioral health facility for worsening psychotic symptoms, paranoid delusion, auditory hallucinations, agitation, and disorganized speech. The patient had no family history of psychiatric illness. The patient expressed no suicidal or homicidal ideations and had no history of substance use, such as alcohol, marijuana, heroin, and cocaine. The patient was initially treated with risperidone and titrated to risperidone 5 mg daily for 2 weeks. The patient's psychiatric condition was improved. However, after a few months of risperidone was initiated, the patient noted that she had stopped menstruating and also reported milky nipple discharge. The patient's pregnancy test was negative. Before beginning risperidone treatment, menses occurred at regular intervals. The patient was evaluated for prolactin levels, thyroid function tests, follicle-stimulating hormone (FSH), luteinizing hormone (LH), estrogen, and progesterone levels; all were within normal limits except prolactin levels. The patient's prolactin level was 44.6 ng/ml (normal range 0-24 ng/ml). Fluphenazine was initiated, and risperidone was discontinued. The patient was psychiatrically stable, but hyperprolactinemia, amenorrhea, and galactorrhea persisted. Fluphenazine was discontinued, and the patient was started on aripiprazole. The dose was titrated up to aripiprazole 20 mg daily. After 2 months, the serum prolactin level decreased to 12.4 ng/ml, and symptoms of hyperprolactinemia (e.g., amenorrhea and galactorrhea) were improved, but the psychiatric symptoms worsened. To address the ongoing psychiatric symptoms, clozapine 150 mg daily was added to the patient's regimen. Following this change in management, the patient's menstruation resumed as expected, and galactorrhea was resolved. The patient was treated with clozapine and aripiprazole for a month with good response and was managing the antipsychotic-induced adverse effect, in this case, hyperprolactinemia.

Case Discussion

Hyperprolactinemia is defined as a condition with a sustained elevation of prolactin above the standard upper limit, the upper limit of 18 ng/ml for men and 24 ng/ml for nonpregnant and nonnursing women [2,9]. Medication-induced hyperprolactinemia typically ranges from 25 ng/ml to 100 ng/ml; this may help distinguish it from a pituitary tumor associated with higher prolactin levels. Nonetheless, some medications, such as risperidone and phenothiazine, can result in prolactin levels exceeding 200 ng/ml. The physiological cause of hyperprolactinemia during pregnancy and breastfeeding is that prolactin levels may rise to 200 ng/ml and 300 ng/ml. Other important differential diagnoses of hyperprolactinemia are cirrhosis, polycystic ovarian syndrome, seizure, and stress [2].

Approximately half of the patients receiving antipsychotic medication may develop hyperprolactinemia compared with 0.4% of the general population. A review of 14 cross-sectional studies, including 2235 people receiving antipsychotics, found the prevalence of hyperprolactinemia ranged from 42%-93% in women and 18%-72% in men [11]. Women of reproductive age are at higher risk of developing antipsychotic-induced hyperprolactinemia than post-menopausal women [8]. Other risk factors of antipsychotic-induced hyperprolactinemia include adolescence, high antipsychotic dose, and specific dopamine D2-receptor gene variants [2].

Mechanism of typical and atypical antipsychotic-induced hyperprolactinemia

Antipsychotics cause hyperprolactinemia by antagonizing dopamine D2 receptors. Dopamine exerts an inhibitory effect on prolactin. Thus, dopamine inhibition increases prolactin release in the hypothalamic tuberoinfundibular tract, inhibiting the release of LH and FSH from the pituitary gland, resulting in low gonadal steroid and hypogonadism [2,8].

Typical antipsychotics are potent D2 receptor antagonists, thus, dissociating from the receptor slowly, resulting in prolog D2 receptor blockade and exerting a cumulative effect on prolactin concentration. By contrast, most atypical antipsychotics dissociate more quickly from D2 receptors. For instance, receptor occupancy for both quetiapine and clozapine falls in the brain, from 60-70% receptor occupancy at 2 hr post-dose to <30% receptor occupancy at 24 hr [10]. It is reasonable to assume lactotroph receptor occupancy changes similarly. Aripiprazole is a partial D2 receptor agonist with high receptor affinity. Its prolonged binding suppresses prolactin secretion [8]. Among atypical antipsychotics, risperidone and amisulpride have a higher ratio of pituitary to striatal D2 receptor occupancy and have a higher propensity to develop hyperprolactinemia [10]. Besides receptor affinity and occupancy, medications with less ability to cross the blood-brain barrier require higher serum concentration for therapeutic effect, thereby increasing the exposure of pituitary D2 receptors resulting in hyperprolactinemia [8].

Risk of developing hyperprolactinemia from different antipsychotics

Management of antipsychotic-induced hyperprolactinemia

General recommendation (Grade D recommendation):

1. Patients with mild and asymptomatic hyperprolactinemia (<50 ng/ml) with the absence of sexual dysfunction, watchful waiting is recommended, and regular checks of serum prolactin at least yearly [13].
2. Moderate to severe hyperprolactinemia (>50 ng/ml), with symptoms/clinical consequences; evaluation for differential diagnosis from specialized service is recommended. Consider MRI if the prolactin level is high or associated with headache and visual field disturbance. After establishing medication-induced hyperprolactinemia, pharmacological intervention should be considered [13,14].

Bushe et al, 2008 and De Berardis et al, 2014

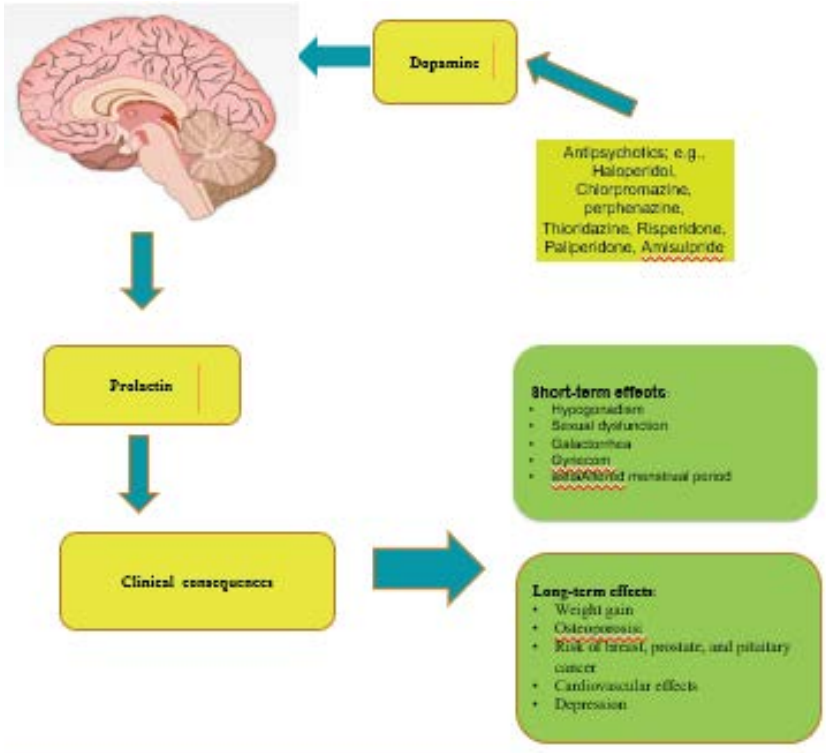

Figure 1. Mechanism of Antipsychotic-induced Hyperprolactinemia ans Short -term & Longterm Clinical Consequecnces

Table 1: Comparison of the First generation (FGA) and Second generation (SGA) antipsychotics. The risk of developing sustained hyperprolactinemia correlates with the potency of D2 receptor antagonism [11,12].

Antipsychotic medications	Potency as D2 receptor antagonists	Sustained Hyperprolactinemia	Transient Hyperprolactinemia
First-generation AP (e.g., haloperidol, chlorpromazine, perphenazine, thioridazine)	+++	Yes	
Risperidone	+++	Yes	
Amisulpride	+++	Yes	
Paliperidone	++	Yes	
Olanzapine	++		Yes
Ziprasidone	+		Yes
Quetiapine	+/-		Yes
Clozapine	+/-		Yes
Asenapine	?/-		
Aripiprazole	-/↓		Yes

Different treatment strategies are [13,14]

a) Decreasing the dose of antipsychotic medication

b) Switching antipsychotic medication (high-risk to low-risk AP). Grade A-C recommendation.

c) Adding aripiprazole (prolactin-sparing agent). Grade A recommendation.

d) Adding dopaminergic agonists (bromocriptine and cabergoline; it is controversial as the risk of worsening psychosis). Grade B recommendation.

e) Treatment with estrogen and testosterone

f) Referral to an endocrinologist

Conclusion

Hyperprolactinemia should be evaluated, especially when signs and symptoms are present in patients receiving antipsychotic treatment. Symptoms of hyperprolactinemia can be bothersome and reason for medication non-compliance. Clinicians should be vigilant about the side effects of antipsychotic medications. Antipsychotic medications with less or no potential to develop hyperprolactinemia should be considered. In this

case, antipsychotic-induced hyperprolactinemia and psychiatric symptoms were managed using atypical antipsychotics like Clozapine and Aripiprazole with a limited dosage.

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