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Hyperprolactinemia in Patients with Psychiatric Illness: A Therapeutic Dilemma

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ABSTRACT

Hyperprolactinemia is a frequently observed condition among psychiatric patients. The causes of hyperprolactinemia can be varied. The most common one being antipsychotic medications and others may include conditions related to prolactin-secreting adenomas (prolactinomas). Dopamine Agonists (DAs) are medications that are commonly used for treating hyperprolactinemic states and prolactinomas. However, lately, there has been concern that DAs might carry a potential for aggravating the psychiatric illness, while antipsychotic medications have been condemned for aggravating hyperprolactinemic states. This review discusses the relationship between the two, and alternative treatment strategies to avoid these potentially serious interactions.

Keywords: Hyperprolactinemia, Anti-psychotic drugs, Prolactinoma

INTRODUCTION

Hyperprolactinemia in patients with psychosis is a common finding in daily clinical practice [1]. A potential bias was noted for testing hyperprolactinemia in patients undergoing neuroleptic treatment [2]. The said patients are also more likely to undergo MRI/CT in this association [2]. It has been recognized, from previous studies, that psychotropic medications are among the most common causes of hyperprolactinemia in general practice [3,4]. Hyperprolactinemia and prolactinomas can cause complications such as irregular menstrual cycles, galactorrhea, and bone loss. Additionally, it can cause specific problems in males such as erectile dysfunction, decreased libido, and gynecomastia. The treatment of hyperprolactinemia, using DAs in patients suffering from psychiatric conditions, has been held accountable for exacerbating or worsening the illness [5]. This review addresses the possible ways to manage hyperprolactinemia observed in psychiatric patients while maintaining the pharmacological psychiatric treatment at the same time.

CASE PRESENTATION

A 48-year-old female, diagnosed as a schizophrenic for 20 years, was admitted to the psychiatry ward of King Khalid University Hospital, Riyadh, to manage her active relapses. The patient has kept off her antipsychotic medications. On admission, she complained of galactorrhea and oligomenorrhea. She was started with risperidone-2 mg orally at night for 4 days and then increased to 4 mg daily. Injectable risperidone (Risperdal Consta-37.5 mg) was also given every 2 weeks. Her initial prolactin level was 6314 miu/l (N 55-425 miu/l), FSH-4.65, LH-2.29, with normal thyroid and renal function tests. A Magnetic Resonance Image (MRI) of the sella turcica revealed a 4 × 8 mm focal pituitary hemorrhagic adenoma. Given the active psychiatric illness and the small-sized macroprolactinomas, the treatment of hyperprolactinemia was postponed until the stabilization of her schizophrenia. Her prolactin level remained almost the same, in the 6000 miu range, during her stay of 4 weeks. She was discharged after the stabilization of her schizophrenia. After 2 months, cabergoline, an ergot derivative, was introduced at a small dose of 0.25 mg weekly. It was subsequently increased to 0.25 mg twice weekly. Her prolactin level dropped to 610 miu/l within 6 weeks, while her menstrual cycle returned to normal and the condition of galactorrhea improved as well.

DISCUSSION

The co-existence of hyperprolactinemia and psychosis is commonly observed in psychiatric patients on antipsychotic drugs. Hyperprolactinemia is presumed to be related to dopamine receptor blockade, mediated by D2 receptors [6-8].

Indeed, it has been documented that the degree of hyperprolactinemia correlates with the degree of occupation of D2 receptors, exceeding by 50% [9]. Many neuroleptic drugs, including risperidone, have been attributed to high prolactin levels [10-12]. It has been reported that the condition is more frequent and severe with regards to first-generation antipsychotic medications [11,12]. These include haloperidol, chlorpromazine, thioridazine, pimozide, thiothhxene, trifluoperazine, and fluphenazine. Second-generation antipsychotics leading to hyperprolactinemia are generally unheard of [11,12]. These include clozapine, lurasidone, asenapine, quetiapine, ziprasidone, and aripiprazole. Be that as it may, of the second-generation antipsychotic medications, risperidone and paliperidone have been associated with prolactin elevation [11,12]. With relevance to risperidone, which was given to the patient in the case study, persistent elevation of prolactin for periods up to 2 years has been documented with maintenance treatment [13]. It is encountered in both men and women and is dose-dependent [11,14]. The hyperprolactinemia in female patients can lead to the emergence of undesirable conditions like galactorrhea, menstrual irregularities, and premature bone loss [4,13]. Concerning men, it might lead to gynecomastia and erectile dysfunction [15,16]. Risperidone-associated hyperprolactinemia was found to adversely affect the patient's health and compliance with the medication [16]. Furthermore, it has been established that the severity of the condition differs based on sex. Women were observed to be more receptible to hyperprolactinemia than men, even with the same dosage [17]. Genetically, risperidone-induced hyperprolactinemia is linked to Taq1A A1 and the A-241G allele of the D2 receptor gene [18].

Prolactin Secreting Adenomas in Patients with Psychiatric Illness

The illustrative case presents the example of a patient who needs to be maintained on antipsychotic medications, which could require treatment with DA for prolactinoma.

Prolactin secreting adenomas account for about 40% of all pituitary adenomas, making them the most common one [19]. The clinical sequelae of prolactinomas could be related to the elevated prolactin level, or to the mass effect of the tumor, particularly when it is more than 1 cm in size (macroprolactinoma). The serum prolactin level correlates with the size of the tumor. Small micro-prolactinomas (<1 cm) are usually treated medically with DAs [20,21]. Generally, these medications are effective in normalizing prolactin levels for up to 70% of cases. Along with that, they can also shrink the size of the adenoma in both micro-prolactinomas and macroprolactinomas [20,21]. Macroprolactinomas can also be treated pharmacologically with the help of Das [20,21]. Surgical treatment or radiotherapy for residual tumor post-surgery is reserved for patients who do not respond to the medical treatment or are intolerant towards dopamine agonists. DAs have many side effects such as nausea, vomiting, orthostatic hypotension, and valvular heart disease (cabergoline doses which are used for the treatment of Parkinson's disease). They have been held responsible for the exacerbation of psychiatric illnesses [22-24].

Pharmacovigilance studies and some case reports have raised concern about the association of antipsychotic drugs especially risperidone with the emergence or enlargement of prolactin-secreting adenomas [25-28]. In the case of a patient with coexisting prolactin-secreting adenoma and active psychosis, the psychiatrist and the endocrinologist must work together in an attempt to manage the clinical consequences of the tumor mass and the resultant hyperprolactinemia, while avoiding the aggravation of the psychiatric disease, which might be instigated due to dopamine agonists. In the circumstance that the prolactinoma is very small while the psychiatric illness is active and severe, it would be wise to give the psychiatric illness the priority of treatment, while observing the hyperprolactinemia and its clinical consequences. For symptomatic patients, a cautious dosage of DA was recommended [29]. On the flip side, this approach has to be undertaken under very close supervision. Others have discouraged this approach due to the possibility of exacerbation of the psychiatric illness during the procedure except if antipsychotic treatment is maintained and under very close supervision [30]. More recently, other countermeasures have been recognized. It is deemed possible to switch to another antipsychotic medication that wouldn't cause an opposing effect on the action of the DA. In a report by Pal and Sarino, olanzapine was successfully used to treat a patient suffering from macroprolactinoma with coexistent bromocriptine therapy [31]. Clozapine combined with quinazoline a DA has also been recommended to treat such patients [32]. In like manner, Quetiapine has also been suggested for the treatment of symptomatic hyperprolactinemia related to antipsychotics [33]. Galactorrhea with normal prolactin levels has rarely been reported with its use [34]. Lately, there have been many reports recommending the use of aripiprazole for treating hyperprolactinemia associated with psychosis and in patients with prolactinomas as well [35-39]. Aripiprazole has unique pharmacological effects of being a potent partial agonist for dopamine D2 and 5-HT1 receptors, but antagonist to 5-HT2A receptors [35-39]. The advantage of using aripiprazole in treating schizophrenia without affecting the prolactin level appears to be due to this partial agonist at D2 receptors. Aripiprazole has a greater affinity for the D2 receptor than risperidone with central D2 receptor occupancy of 90%-95% at doses of 15 mg/day [36,40,41]. On the occurrence of hypodopaminergic activity

caused by risperidone, aripiprazole will function as a dopamine agonist at postsynaptic receptors [41]. In a report by Casey, et al. it was possible to safely switch patients to aripiprazole with the help of three different strategies. The first option is immediate initiation of 30 mg/day and discontinuation of the current antipsychotic medication. The second option is tapering down the antipsychotic treatment over 2 weeks while immediately initiating aripiprazole at 30 mg/day dosage. The third is by gradually building up the dose of aripiprazole over 2 weeks while simultaneously tapering down the dose of the current antipsychotic medication [42]. Careful monitoring of the psychiatric and endocrine status is warranted for all three approaches. In some case reports, prolactin elevation was also found with aripiprazole treatment, particularly at a higher dosage [43,44]. A dose of 5 mg was suggested as an appropriate starting dose for this setting, with the increment of 5 mg by week 4 of treatment as tolerated [45].

Use of Dopamine Agonists in Psychiatric Illness

If the antipsychotic medication-induced hyperprolactinemia is asymptomatic, there is no need to discontinue the treatment [29,46]. If in any case, hypogonadal symptoms are discovered, replacement with estrogen or testosterone may be needed [29]. Regardless, there have been reports of safe and successful treatment of hyperprolactinemia with dopamine agonists while the patients were on antipsychotic medications as well.

Risperidone-induced hyperprolactinemia in children was successfully reversed with cabergoline [47]. Furthermore, the effective and safe use of cabergoline and bromocriptine in adult patients suffering from risperidone-induced hyperprolactinemia was also reported with no worsening of the psychiatric illness [48-50]. This approach can be considered as the last option when a drug that does not cause hyperprolactinemia cannot be substituted for the asymptomatic hyperprolactinemic patient [29]. However, this issue is still a matter of debate as it has not been endorsed by other investigators [51].

CONCLUSION

The treatment of hyperprolactinemia in a psychiatric patient requires proper judgment; taking into account the clinical backdrop of the patient, the presence or absence of symptoms, and the formation of the prolactinoma tumor. For patients that suffer from prolactinoma and psychosis simultaneously, special attention should be paid to tackle the psychiatric illness while managing the prolactin-secreting adenoma and its consequences at the same time. Cooperation between the psychiatrist and the endocrinologist is necessary, and a few feasible therapeutic options are available. A small asymptomatic microadenoma can be monitored without intervention whilst priority is given to psychiatric treatment [30]. In the case of symptomatic prolactinoma or more sizable adenomas, switching to another medication such as aripiprazole might be favorable while either maintaining or tapering down the antipsychotic treatment. Careful and small doses of dopamine agonists preferably cabergoline can be considered while conducting a close follow-up of the psychiatric illness [30]. In antipsychotic-induced hyperprolactinemia, the first step to undertake is reducing the dosage or switching to a prolactin-sparing antipsychotic medication. Only if that is not possible, the smallest feasible dose of DA can be contemplated with a very close observation of the psychiatric illness. If hyperprolactinemia is mild and the patient is asymptomatic, treatment with the antipsychotic drug can be continued. As stated above, some issues in managing such cases are still controversial. More studies are required to guide practicing clinicians for the safe management of these patients.

DECLARATIONS

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Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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