

Amenorrhea as a Side Effect of Low Dose Aripiprazole: An Adolescent Case

Gulen Guler¹, Meryem Ozlem Kutuk², Halil Kara³

¹Department of Child and Adolescent Psychiatry, Elazig Mental Health Hospital, Elazig, ²Department of Child and Adolescent Psychiatry, Baskent University Medical Faculty, Adana, ³Department of Child and Adolescent Psychiatry, Aksaray State Hospital, Aksaray, Turkey

Amenorrhea, oligomenorrhea, galactorrhoea, gynecomastia, infertility, and sexual dysfunction may arise as a consequence of hyperprolactinemia. Hyperprolactinemia is one of major side effects of treatment with antipsychotics, but aripiprazole is known as a dopamine stabilizer antipsychotic which can be used to improve hyperprolactinemia. In this report, it was described that an adolescent patient experienced amenorrhea after adding very low dose aripiprazole to ongoing fluoxetine treatment regime for major depressive disorder. Additionally, this case showed that the patient recovered from the amenorrhea with replacement of aripiprazole with quetiapine.

KEY WORDS: Adolescent; Amenorrhea; Aripiprazole.

INTRODUCTION

Hyperprolactinemia, a condition of elevated serum prolactin, is usually the major side effect of treatment with typical antipsychotics and some atypical antipsychotics. Clinical abnormalities such as amenorrhea, oligomenorrhea, galactorrhoea, gynecomastia, infertility, and sexual dysfunction may arise as a consequence of hyperprolactinemia. Typical antipsychotics and some atypical antipsychotics, such as risperidone and amisulpride, have been reported to be associated with hyperprolactinemia due to strong antagonists of D2 receptor.¹⁾ Aripiprazole is a known dopamine stabilizer antipsychotic, which acts as a partial agonist of D2 receptor and a strong antagonist of 5HT2A receptor. It has been reported that inclusion of aripiprazole to an ongoing treatment regime or prescription of aripiprazole alone improves hyperprolactinemia.^{2,3)}

This paper analyzes a case study of an adolescent pa-

tient with amenorrhea due to hyperprolactinemia. She was under fluoxetine and low dose aripiprazole treatment for major depressive disorder. Interestingly, this study showed that the patient recovered from the amenorrhea with replacement of aripiprazole with Quetiapine.

CASE

Our study presents an interesting case of a seventeen-year-old girl who was referred to the child psychiatry clinic with symptoms of depression and suicide attempt by taking medical pills. The patient was transferred to institutionalized care owing to intra-familial events. She had consistent problems of adaptation to the institutional surroundings and could not get along well with other children. As a result, she did not attend the school and displayed aggressive behaviours. At the initial psychiatric evaluation, she looked tired and sad with untidy hair and unkempt clothes. Her mood was clearly depressive and consistent with her affect. During the interview, she was reluctant, had minimal eye contact and answered with a subdued voice. She explained the reason for her suicidal behaviour that she blamed her loneliness and stated that she could not stand living anymore. During interview, no active suicidal ideations, delusions or hallucinations was observed. During the first interview, Beck Depression

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Address for correspondence: Gulen Guler, MD

Department of Child and Adolescent Psychiatry, Elazig Mental Health Hospital, Rizaiye Mah, Kazim Hoca Street No: 23/B, Elazig 23100, Turkey

Tel: +90-424-238-79-53, Fax: +90-424-212-78-31

E-mail: dr.gulen@hotmail.com

ORCID: <https://orcid.org/0000-0001-9555-3916>

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score was 44, State-Trait Anxiety Inventory (STAI)-1 score was 40 and STAI-2 score was 38. Based on Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) criteria, she was diagnosed with Major Depressive Disorder and treatment with fluoxetine (20 mg/day), and aripiprazole (5 mg/day) was started. Two months after the initiation of the treatment, fluoxetine was doubled (40 mg/day) and this treatment regime was continued for subsequent four months, with aripiprazole (5 mg/day). This resulted in regression of depressive symptoms. During the next follow-up interview, she reported not having menstrual cycles for the past four months. Therefore, she was referred to an obstetrician immediately. She had no reports of menstrual irregularity, hirsutism, drug use or history of any related medical disorder prior to the treatment. There, she underwent pelvic ultrasonography examination which showed normal ovaries and endometrium. Analysis of blood test reports showed normal functions of thyroid, liver and kidney. Her pregnancy test was also negative. No pathology was detected in cranial magnetic resonance imaging. Finally, the pathology was reasoned to very high prolactin level in blood serum, which was shown to be 74 ng/ml, while the normal range being 4-20 ng/ml. After ruling out other possible causes of hyperprolactinemia, aripiprazole treatment was thought to be responsible for the observed symptoms. As an immediate change in therapy, aripiprazole was replaced with quetiapine (200 mg/day). Aripiprazole replacement successfully resulted in reduction of blood prolactin levels to 17 ng/ml and menstrual cycle returned to normal after two months of quetiapine treatment.

DISCUSSION

Aripiprazole, unlike other antipsychotics, is a partial dopamine antagonist which reduces prolactin response to anti-psychotic drugs. Adjunctive aripiprazole is a treatment option for second generation antipsychotic-induced hyperprolactinemia in youth who is stable on monotherapy.⁴⁾ Interestingly, it acts as an agonist at lower doses, whereas it has an antagonist effect at high doses. It has been reported that plasma prolactin level rises with an increasing dose of aripiprazole and amenorrhea might develop at doses higher than 12 mg/day.⁵⁾ Several reported cases link hyperprolactinemia with aripiprazole.

Mendhekar and Andrade⁶⁾ has reported that increased dose of aripiprazole results in extrapyramidal side effects and galactorrhoea as early as two weeks after treatment in a 36-year-old schizophreniform patient. In another case study, Joseph⁷⁾ reported the development of hyperprolactinemia after aripiprazole (both 10 mg and 15 mg per day) intake in 36-year-old patient with delusional disorder. In both of these cases, no pharmacological agent other than aripiprazole was used. In another case, Saraf *et al.*⁸⁾ reported the development of hyperprolactinemia as a consequence of treatment with lithium in combination with aripiprazole (15 mg/day) in a 18-year-old girl with bipolar disorder. The treatment was carried out for three months. Subsequent replacement of aripiprazole with quetiapine resulted in alleviation of hyperprolactinemia. Another case of a 21-year-old patient, who used sertraline and aripiprazole (10 mg/day) for psychotic major depressive disorder, also reported the development of amenorrhea and galactorrhoea within three months of intake.⁹⁾ In all of the above mentioned cases, hyperprolactinemia was attributed to relatively high aripiprazole dosage.

In a 29-year-old female patient of schizoaffective disorder, tenderness and galactorrhoea developed in the breast when aripiprazole (15 mg/day) was added to treatment. The patient was previously under valproate, biperiden, and haloperidol treatment. Subsequently haloperidol dose was reduced and aripiprazole was added to the treatment regime. After detection of galactorrhoea the drug was removed from the prescription. The induction of hyperprolactinemia and galactorrhoea by aripiprazole was interpreted as an idiosyncratic reaction as there is no known mechanism to explain this effect.¹⁰⁾

Here we report the definite induction of amenorrhea after fluoxetine (40 mg) and aripiprazole (5 mg) administration. We have also demonstrated the alleviation of amenorrhea through the replacement of aripiprazole with quetiapine. Combined use of aripiprazole with fluoxetine might explain the development of hyperprolactinemia at such a low dose of these medications. Aripiprazole acts as a substrate for CYP2D6, whereas fluoxetine is a strong inhibitor of CYP2D6.¹¹⁾ Fluoxetine might lead to emergence of secondary hyperprolactinemia, by inhibiting CYP2D6 and increasing the level of aripiprazole in blood plasma. Quetiapine is metabolized through CYP3A4.¹²⁾ As quetiapine does not lead to hyperprolactinemia, it can be considered as an appropriate alternative to aripiprazole for

the treatment of various psychotic disorders. On the other hand, interestingly, a case of very low dose quetiapine-associated euprolactinemic galactorrhea in combination of venlafaxine was reported in a 33-year-old Korean woman. The mechanism of this side effect is unclear, drug interaction is ruled out because of the metabolites of quetiapine have little inhibitory effect on the cytochrome P450 systems.¹³⁾

In the literature, not too much knowledge about hyperprolactinemia with selective serotonin reuptake inhibitors, it was reported that a female obsessive compulsive disorder patient has hyperprolactinemic galactorrhea with treatment of fluoxetine.¹⁴⁾ In our case report, hyperprolactinemic amenorrhea is not only due to fluoxetine, our case is associated with drug-drug interaction between fluoxetine and aripiprazole. It should not be ignored that hyperprolactinemia and other side effects of aripiprazole may occur more aggressively in combinatorial medications due to interactions among medications.

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