Report

Case Report of Refractory Hyperhomocysteinemia Related to the Antipsychotic Drug Olanzapine

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ABSTRACT

Background: Hyperhomocysteinemia is a metabolic disorder linked to cardiovascular diseases, neurological disorders, and pregnancy complications. Olanzapine, a widely used antipsychotic, is recognized for its association with metabolic abnormalities; however, its connection to refractory hyperhomocysteinemia remains unclear.

Case presentation: The patient experienced a significant increase in blood homocysteine levels (> 150μmol/L) due to infertility and was unable to reduce them to normal (<10 μ mol/L) despite treatment with up to 6g/day of betaine, high-dose B vitamins, and methocobalamin. Long-term administration of olanzapine (5mg/day) was found to be associated with the condition, and levels decreased briefly after switching to aripiprazole (94 μ mol/L).However, due to serious adverse reactions, the use of alanzapine was resumed, resulting in an increase in blood homocysteine levels once again (113~125 μ mol/L). Genetic testing revealed a homozygous mutation at MTHFR 1298, and intensive complementary therapy along with a strict low-protein diet resulted in fluctuating levels of 100~150μmol/L.. The patient was ultimately managed successfully through in - vitro fertilization (IVF), but continuous treatment with olanzapine led to long-term non-remission of hyperhomocysteinemia.

Conclusion: This case suggests that olanzapine may exacerbate metabolic disorders by interfering with methylation cycling, and that genetic factors (e.g., MTHFR mutations) may become more refractory. Multidisciplinary collaboration is needed to balance the treatment and metabolic management of neurological disorders, and to further explore mechanisms and optimize intervention strategies in the future.

INTRODUCTION

Hyperhomocysteinemia is a metabolic disorder characterized by elevated levels of homocysteine in the blood (2, 3). It has been associated with various adverse health outcomes, including cardiovascular diseases, neurological disorders, and pregnancy complications (4). Antipsychotic medications are extensively utilized in the treatment of psychotic disorders. Notably, olanzapine has been reported to be intricately associated with metabolic disturbances (5). However, the relationship between olanzapine and refractory hyperhomocysteinemia remains relatively understudied. This case report aims to describe a patient with hyperhomocysteinemia that was refractory to conventional treatment and was potentially related to the

use of olanzapine, providing insights into the possible association and management challenges.

PRESENT ILLNESS HISTORY

In April 2022, during an infertility examination, the patient was detected to have hyperhomocysteinemia, with an initial value as high as over 150μmol/L. Subsequently, the local doctor prescribed betaine at a dosage of 1g/day. As a result, the value decreased to over 110μmol/L, yet it still remained far above the normal reference value (the normal range is 10) (1). In an attempt to further reduce the homocysteine level, the dosage of betaine was increased to 3g/day, in combination with one tablet of multivitamin B complex and mecobalamin 0.5mg. However, a subsequent examination half a month later still revealed a high level of 115. Consequently, the dosage of betaine was further escalated to 4g/day. Nevertheless, after another half - month, the value still did not show a downward trend.

Upon inquiring into the medical history, it was discovered that the patient was concurrently taking the antipsychotic drug olanzapine at a dosage of 5mg/day at that time. There was a strong suspicion that the hyperhomocysteinemia was associated with olanzapine, and it was recommended that the drug be changed. After consultation with the psychiatrist, olanzapine was replaced with aripiprazole at a dosage of 5mg/day. Half a month later, the homocysteine level dropped to 94 μ mol/L. However, due to severe insomnia and other adverse conditions induced by aripiprazole, on May 25th, as advised by the psychiatrist, aripiprazole was switched back to olanzapine, one tablet per day, and the patient was instructed to maintain the antipsychotic drug without change for one month to achieve stabilization. The medications during this period included betaine 4g per day, one tablet of mecobalamin, one tablet each of vitamin B6 and B12, along with olanzapine 5mg.

On June 22nd, the homocysteine value increased to 113.37 μ mol/L. Subsequently, the medication regimen was adjusted as follows: betaine 6g/day; folic acid tablets 5mg/day; B1 10mg/day; B6 30mg/day, B12 75mg / day; mecobalamin 1.5mg/day. Additionally, the patient was advised to strictly control protein intake, with a near - complete abstention from meat, eggs, and dairy products. On July 20th, the homocysteine test result was 125.04 μ mol/L.

Subsequently, owing to the inability to discontinue olanzapine, the above - mentioned medications were continuously maintained, and the homocysteine level has been fluctuating within the range of 100 - 150μmol/L. Two years later, this patient successfully achieved pregnancy through in - vitro fertilization (IVF) and gave birth to a healthy baby boy. However, because she has been continuously taking olanzapine, her homocysteine level has remained persistently elevated.

PAST MEDICAL HISTORY

The patient has a history of mental illness and had been taking olanzapine for a long time to control the condition(2, 3)
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PHYSICAL EXAMINATION

Infertility(4, 5). Height: 176cm, Weight: 69kg, The development is normal, and the general condition is good.

LABORATORY TESTS

Folic acid gene polymorphism test: MTHFR 677 locus cc wild type, 1298 locus CC (AA wild type) homozygous mutation. Other biochemical tests: liver and kidney function, thyroid function, etc. were all within the normal

range. 25-hydroxyvitamin D3 was 55.8, calcitonin was 0.040, and intact parathyroid hormone was 19.3. Carotid artery ultrasound examination did not detect the formation of masses.

DISCUSSION

In this case, the patient presented with extremely high levels of homocysteine, which were refractory to dose escalations of betaine and supplementation with B - vitamins. The temporal relationship between the adjustment of olanzapine and changes in homocysteine levels strongly suggested a potential causal link. When olanzapine was replaced with aripiprazole, a significant decrease in homocysteine levels was observed, while the readministration of olanzapine led to a subsequent increase (6, 7).

The mechanism underlying the association between olanzapine and hyperhomocysteinemia may be complex. Olanzapine has been shown to affect various metabolic pathways. Research reports that oxidative stress may increase homocysteine levels in patients treated with olanzapine, as it might interfere with the methylation cycle, which is crucial for homocysteine metabolism (8, 9). The MTHFR gene mutations detected in this patient, although not directly related to the effect of olanzapine, could have further complicated the homocysteine metabolism and contributed to the refractoriness of hyperhomocysteinemia (7).

The management of this patient was challenging. Despite aggressive vitamin supplementation and dietary control, the homocysteine levels remained persistently elevated due to the necessity of maintaining olanzapine treatment for mental illness(10). This highlights the need for a comprehensive approach in patients with such comorbidities, involving close collaboration between psychiatrists and physicians in other specialties. Future research is warranted to further explore the mechanisms of this association and to develop more effective strategies for managing hyperhomocysteinemia in patients on olanzapine treatment.

CONCLUSION

This case suggests that olanzapine may exacerbate metabolic disorders by interfering with methylation cycling, and that genetic factors (e.g., MTHFR mutations) may become more refractory. Multidisciplinary collaboration is needed to balance the treatment and metabolic management of neurological disorders, and to further explore mechanisms and optimize intervention strategies in the future.

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